SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS

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Dr. Tarun Varshney…

ABBREVIATIONS

BCAA	Branched-chain amino acid
BMI	Body mass index
CT	Computed tomography
CTP	Child turcotte pugh
EWGSOP	European working group on sarcopenia
GCN	General control of nutrition
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIF	Hypoxia inducible factor
IGF	insulin-like growth factor
INR	International normalized ratio
MELD	Model for end stage liver disease
MRI	Magnetic reasonance imaging
mTOR	Mammalian target of rapamycin
NASH	Nonalcoholic steatohepatitis
PCM	Protein-calorie malnutrition
PDH	Pyruvate dehydrogenase
PDK	Pyruvate dehydrogenase kinase
SMI	Skeletal muscle index
TCA	Tricarboxylic acid
TGF	Transforming growth factor
UGI	Upper Gastrointestinal
αKG	α-ketoglutarate

ABSTRACT

Introduction: Sarcopenia is characterized by the loss of skeletal muscle mass, strength and performance. Sarcopenia is associated with higher rates of sepsis, gastrointestinal bleeding and hepatic encephalopathy. Treatment of sarcopenia improves the prognosis of patients with liver cirrhosis, in general and post-transplant also.

Aim: The study aimed to assess survival rate, complications, Prevalence in patients with liver cirrhosis with sarcopenia. Assessment of sarcopenia was assessed by using sarcopenia indices, Computerized Tomography Skeletal muscle index (SMI), Handgrip Strength (HGS) and Gait velocity in patients with liver cirrhosis.

Methods: The Inclusion criteria were: All adults with liver cirrhosis. All patients with advanced stages of hepatocellular carcinoma, hepatic coma with acquired immunodeficiency syndrome, pancreatic insufficiency, patient receiving enteral nutrition and pregnancy and lactation. Sarcopenia indices were compared between survivor and non survivor patient with liver cirrhosis. The Survival of patients at 6 months was the primary outcome of study. All analysis was carried out by using SPSS version 21 software.

Results: One hundred and sixty one patients (121 were males and 40 were females) of liver cirrhosis were enrolled in this study. One thirty one (81.36%) patients of Sarcopenia were found in the present study. The prevalence of sarcopenia were significantly greater in males ($p<0.01$). There was significance difference in gait velocity (m/s) in survivors, 0.66±0.20 vs. expired, 0.53±0.15 ($P<0.0001$). These was significance difference in Handgrip strength (dynes/cm^2) in survivors, 20.24±7.88 vs. expired, 15.01±6.84 ($p=0.000$). Complication of Cirrhosis, Ascites were significant higher in males vs. females ($P=0.043$).

Conclusion: The current study is the most comprehensive study that gives the impacts of sarcopenia in patients with compensated and decompensated liver cirrhosis. The prevalence of Sarcopenia was 81.36% in patients with liver cirrhosis. Sarcopenia impacts Survival in presence of complication such as ascites, hepatic encephalopathy and variceal bleeding).

Keywords: Sarcopenia, Gait velocity, Handgrip Strength, SMI.

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INTRODUCTION

Protein-calorie malnutrition (PCM) and/or sarcopenia, and variety of nutritional disorders are frequently observed in patients with liver cirrhosis as liver is an organ central to nutrient metabolism.[1] PCM is associated with high morbidity and mortality due to an increased risk of complications in these patients.[2,3] Therefore, diagnosis of and intervention for PCM are essential to improve the outcome of patients with cirrhosis. Nutritional support, including branched-chain amino acid (BCAA) supplementation and frequent meals, is recommended by current guidelines.[4]

Sarcopenia is characterized by the depletion of skeletal muscle mass, and is a predictor of morbidity and mortality in patients with Liver Cirrhosis.[5,6] Skeletal muscle mass is generally maintained by a balance between protein synthesis and protein breakdown. Cirrhotic patients have insufficient glycogen stores due to liver atrophy, and their energy generation pattern after an overnight fast is equivalent to that observed in healthy individuals after 2 to 3 days of starvation.[7] Such a catabolic state increases the consumption of amino acids as an energy source and accelerates the breakdown of skeletal muscle to release amino acids, resulting in sarcopenia.[8] Hence, a nutritional intervention can be an effective modality for improving sarcopenia associated with Cirrhosis.[9,10]

Predicting prognosis is crucial in the management of patients with cirrhosis. A number of prognostic models have been derived and validated. Since 2002, the MELD score has replaced the CTP score for organ allocation in patients waiting for Liver Transplantation in the United States, due to the advantage of including only objective laboratory variables and its superior ability to predict short-term outcomes compared to the CTP score. However, the MELD score also has some drawbacks, including variability in laboratory parameters, misclassification of some patients with a low MELD score, and the lack of a nutritional status assessment.[11]

Many researchers have tried to improve the prognostic performance of the MELD score. Hyponatremia accurately predicts short-term mortality independently of the MELD score and is often associated with ascites, hepatorenal syndrome, and liver-related mortality.[12] Incorporating serum sodium into the MELD score, known as MELD-Na, improves its predictive ability, particularly for patients with a low MELD score.[13]

In some reports, CTP or MELD scores were predictors of sarcopenia, whereas others found that sarcopenia was not correlated with the degree of liver dysfunction assessed by conventional scoring systems (CTP or MELD score).[14]

Sarcopenia is an important prognostic factor in cirrhosis. Malnutrition is one of the most frequent complications in patients with cirrhosis, and it adversely affects other complications, quality of life, survival, and outcome after liver transplantation.[15] Despite its high prevalence and important prognostic role, muscle wasting or sarcopenia, which is a major feature of malnutrition, has not been highlighted until recently. Nutritional assessment is therefore crucial for identifying patients at risk or with already established malnutrition and refer them for nutritional intervention and support.

In the current literature, nutritional assessment of cirrhotic patients is performed using several tools and methods. However their accuracy is widely affected by the underlying disease and its complications. Studies on nutritional assessment in cirrhosis usually focus on one or few aspects of nutritional status and not on a full nutritional assessment combining information from medical, biochemical, nutritional, and body composition variables. Sarcopenia is highly prevalent and an independent prognostic factor for mortality in patients with cirrhosis.[16-20] Adding muscle wasting to the currently accepted prognostic scores has shown promising results.[21] Therefore, sarcopenia quantified by an objective method combined with commonly used prognostic systems has the potential to improve prognostication of patients with cirrhosis.

Hence, the present study aims at a thorough assessment of the nutritional status of cirrhotic patients using standardized methods to estimate the prevalence of sarcopenia in patients of liver cirrhosis. The

current study also aims to assess complications and survival rate in patients of liver cirrhosis with sarcopenia.

AIMS AND OBJECTIVES

1. To assess the survival rate of patients of liver cirrhosis with sarcopenia.
2. To assess complications in patients of liver cirrhosis with sarcopenia.
3. To assess prevalence of sarcopenia in patients of liver cirrhosis.

REVIEW OF LITERATURE

Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death.[22,23] The EWGSOP European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. Thus, diagnosis requires documentation of criterion 1 plus documentation of either criterion 2 or criterion 3 (Table 1). The rationale for use of two criteria is: muscle strength does not depend solely on muscle mass, and the relationship between strength and mass is not linear.[23,24] Thus, defining sarcopenia only in terms of muscle mass is too narrow and may be of limited clinical value.

Table 1: Criteria for the diagnosis of sarcopenia

1.	Low muscle mass
2.	Low muscle strength or quality
3.	Low physical performance

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or Criterion 3)

Sarcopenia in cirrhosis

Loss of skeletal muscle mass or sarcopenia is the most common complication of cirrhosis and adversely affects survival, quality of life, outcome after liver transplantation, and response to stress including infection and surgery.[25] Cachexia and sarcopenia are recognized as a major complication of a number of chronic diseases including cancer, chronic obstructive pulmonary disease, chronic heart failure, and chronic renal failure.[25-28] It is interesting that there has been little focus on the prevalence, impact therapy of sarcopenia and cachexia in cirrhosis, especially given that the liver is the most metabolically active organ that regulates and interacts with the skeletal muscle and adipose tissue to form a “metabolic organ complex”.[29,30]

A. Epidemiology of sarcopenia in cirrhosis

Cross-sectional imaging studies have reported that the prevalence of sarcopenia is 30%-70% among patients with cirrhosis. This wide range is partly explained by the lack of an operational definition for sarcopenia in patients with cirrhosis, patient baseline characteristics, and diversity in the cause and severity of liver disease among studies Sarcopenia is more frequent in men than in women and in patients with a low BMI. The proportion of patients with sarcopenia is higher in those with alcoholic liver disease (80%) compared to other diseases (31%-71%).

Data from the Centers for Disease Control in 2006 showed that the annual incidence of cirrhosis is 72.3 per 100,000 population with an annual mortality rate of 27,000.[31] Additional data support similar prevalence rates of cirrhosis both in the Western hemisphere and globally.[31–36] With the assumption of the baseline prevalence of 0.15%, the total number of cirrhotics in the USA in 2006 is estimated to be 2.5 million. Data from the organ procurement and transplant network that the prevalence of cirrhosis is progressively increasing based on the new patients added to the active and inactive waiting lists.[37] Given the background of these staggering numbers, it is important to underscore the fact that the increase in annual liver transplant rates (17.42 to 22.29/million population) has not kept pace with the increase in numbers of patients with cirrhosis (Scientific Registry of Transplant Recipients (SRTR): 2009 OPTN/SRTR Annual Report 1999-2008. HHS/HRSA/HSB/DOT). Using the highest liver transplantation rate of 22.29/million (in 2006), the number of nontransplanted Cirrhotics would increase by about 14,000/year based on the US population assumption of 300 million, without taking into account the projected increases related to hepatitis C and nonalcoholic fatty liver disease.[32] Using these very conservative figures, the nontransplant management of cirrhosis will be required for over 2.5 million patients by the end of this decade. The goals of this approach are to increase transplant free survival, decrease the risks of complications, and improve quality of life especially since a reduced

post transplant quality of life is being increasingly recognized.[38-41] Malnutrition has been reported in 60–80% of patients with cirrhosis, but when sarcopenia was specifically evaluated, it occurred in about 40 % of cirrhotics.[42,43] Transplant free survival depends on the severity of the underlying liver disease as well as management of the complications of cirrhosis.[44] Oesophageal varices are present in 30–60% of patients with cirrhosis. Refractory ascites occurs in 5–10% of patients and spontaneous bacterial peritonitis occurs in about 30% of patients with ascites.[44] Hepatorenal syndrome occurs in about 8% of cirrhotic patients with ascites. Portopulmonary hypertension and hepatopulmonary syndrome occur in about 0.5–5% of cirrhotics. The annual incidence of hepatocellular carcinoma is 1.4% in compensated and 4% in decompensated cirrhosis. Extensive studies have been published on these complications as of September 30, 2011 and the unfiltered numbers of human studies published and indexed in PUBMED are shown in Table 2. As can be seen, the number of publications on sarcopenia in cirrhosis is very small and if the search term is expanded to cachexia or malnutrition, the number of publications is higher but the studies are no longer specific to muscle loss.

Table 2: Number of publications retrieved on PUBMED

Number of publications retrieved on PUBMED using the search terms limited for "human"	
Search term	**Number of publications on PUBMED**
Cirrhosis, ascites	5,633
Cirrhosis, hepatic encephalopathy	2,870
Cirrhosis, portal hypertension	8,675
Cirrhosis, hepatocellular carcinoma	11,963
Cirrhosis, sarcopenia	8
Liver, sarcopenia	16
Cirrhosis, liver, cachexia	46
Cirrhosis, liver, malnutrition	1000

B. Malnutrition and its specific components in cirrhosis

The major problems with the term “malnutrition in cirrhosis” is the lack of focus on the specific components that constitute malnutrition, i.e., sarcopenia, loss of visceral or subcutaneous adipose tissue mass, alteration in substrate utilization and disordered energy metabolism, and a combination to varying extent of these disorders. One definition for malnutrition that has been proposed is that it is “a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrient causes adverse effects on body composition, function and outcome”.[45] The limitation of this definition is that it lacks specifics when it comes to the definition or terminology, especially in the background of advanced liver disease. Recent attempts to arrive at a consensus definition for sarcopenia, cachexia, and precachexia have focused on nonhepatic diseases, aging, and cancers. However, these definitions and the underlying mechanisms may need to be modified in patients with cirrhosis. A number of complex metabolic alterations occur in liver disease that are unique to cirrhosis and affect the skeletal muscle growth and atrophy responses. These include dysregulation of fatty acid oxidation and ketogenesis, gluconeogenesis from amino acids, glycogenolysis, and selective utilization of aromatic amino acids in the liver and branched chain amino acids in the skeletal muscle as a source of energy.[46,47] A number of biochemical, cytokine, hormonal, and neurological abnormalities in advanced liver disease are also similar to those in other chronic disorders.[48] Therefore, it is essential to have a consensus definition for the terms precachexia, cachexia, and sarcopenia in cirrhotic patients that has common features with other chronic diseases and certain essential differences. Inclusion of patients with cirrhosis while such definitions are being generated will assist in both consilience and translation of the rapid advances occurring in the field of myology and nutrition into clinical application for these patients. Sarcopenia is characterized by loss of muscle mass and has been used to define the loss of muscle mass in aging even though it is now being used in other disease states. Cachexia is defined as loss of both fat and muscle mass.[49-51] Additional terms that

have been used include precachexia that is defined by the unintentional weight loss of <5% of usual bodyweight in the last 6months, in the background of an underlying chronic disease, while sarcopenic obesity is used to refer to the disproportionate loss of muscle mass in the presence of increased adipose tissue mass.[51] Missing are clear generalizable definitions and establishment of normal values. Most publications use historical norms and younger subjects to define sarcopenia that may not necessarily reflect the patient population.[52,53] The potential of historical controls having different growth patterns, adipose tissue, and muscle mass in adulthood needs to be addressed. Additionally, the large-scale changes in the population demographics, mobility, and ethnicity are likely to affect the normative values. Furthermore, a recent comment that one of the hallmarks of cachexia is that loss of lean body mass cannot be prevented or reversed by simply increasing nutritional intake is of critical importance in the management of cirrhotic patients since neither cachexia nor sarcopenia is clearly defined in the cirrhotic population, but they do suffer from either or both.[54] Given the absence of standardized terminology in patients with liver disease, there is a compelling need to define these terms taking into consideration, the metabolic abnormalities specific for cirrhosis. Finally, it must be reiterated that even though the signaling pathways responsible for regulation of skeletal muscle mass are altered, it is not clear if the same alterations occur in all chronic noncommunicable diseases.[55,56]

C. Clinical impact of sarcopenia, cachexia, and malnutrition in cirrhosis

Since liver transplantation is not available or necessary for the majority of cirrhotics, nontransplant options are required and the end points for the therapy of these patients need to be redefined to improve quality of life, prevent and treat complications, and potentially extend survival.[40,41] Using the published prevalence data, the total number of cirrhotic patients with reduced muscle mass is about 1.25 million. Sarcopenia is the most common complication of cirrhosis with very limited data on the mechanisms responsible for it and few treatment

options.[42] It contributes to the aggravation of other complications of cirrhosis including encephalopathy, ascites and portal hypertension.[47,57-62] It is also the major contributor to impaired quality of life in these patients.[63] In contrast to the very limited literature on sarcopenia or muscle loss in liver disease.[42,43] There is an explosion of data on sarcopenia in aging and molecular mechanisms of regulation of muscle loss and re-growth.[49,64] Unfortunately, these very interesting and exciting advances in the field of muscle biology have had very limited translation into human cirrhosis. Our recent preliminary data that an increase in muscle mass[65] is likely to improve survival provides an impetus for rapid translation to clinical use of many of the novel concepts in skeletal muscle loss including the role of satellite cells, autophagy, myostatin regulation of muscle mass, proteolytic pathways, metabolic regulation of muscle protein kinetics and the molecular regulation and integration of protein synthesis, breakdown, and satellite cell-mediated regeneration.[56,66]

D. Potential mechanisms of sarcopenia and cachexia in cirrhosis

Cirrhosis is a form of end-stage liver disease that is the culmination of a number of chronic liver disorders. Since there is no therapy to reverse the fibrosis, hepatocellular dysfunction and vascular remodelling in cirrhosis, management has focused on treating the aetiology of the liver disease, prevention and therapy of the complications, and replacing the diseased liver by transplantation. Liver transplantation is curative for cirrhosis; this therapeutic option does not exist for the majority of patients.[67] Therefore, nontransplant therapeutic options remain the primary management option with the need to focus on reduced muscle mass because of its clinical relevance.

Even though a large number of descriptive studies show the high clinical significance of sarcopenia in cirrhosis, mechanistic studies to identify how sarcopenia develops and the mediators of the liver muscle axis are much less well understood. Early studies have suggested that patients with cirrhosis have a number of reasons for malnutrition, primarily muscle loss, but the most important reasons are poor oral

intake and lack of activity. However, 2 meta-analyses have suggested that supplemental nutrition does not improve clinical outcomes.[15] This is because patients with liver disease are believed to be in a state of anabolic resistance that prevents appropriate skeletal muscle responses to nutrient administration. Skeletal muscle mass is maintained by a balance between protein synthesis, breakdown and possibly the regenerative potential mediated by the myogenically committed stem cells, satellite cells. Studies in the portocaval anastomosis rat provided an explanation for human findings. Early after the anastomosis, there was increased skeletal muscle proteolysis with unaltered protein synthesis and later in the course, both protein synthesis and proteasome mediated proteolysis were lower. Interestingly, autophagy was increased in the muscle of cirrhotics even when ubiquitin mediated proteolysis was unaltered or decreased. A recent study reported lower protein synthesis markers in the skeletal muscle of patients with cirrhosis with decreased ubiquitin mediated but increased autophagy mediated proteolysis.[16] These data show that reduced protein synthesis and increased autophagy mediated protein breakdown contribute to ongoing skeletal muscle loss in cirrhosis.

D.1 Metabolic studies show altered whole body protein turnover in cirrhosis

As mentioned earlier, studies to date have used isotopic tracer methodology and descriptive and correlation studies to explain the development of “malnutrition” in cirrhosis. Isotopic tracer studies have shown that whole body protein breakdown is increased, unaltered, or decreased.[67-71] Indirect measures of whole body protein synthesis have been either unaltered or decreased.[69-71] Additionally, rates of albumin synthesis that have been used in other chronic disorders are a poor measure of nutrient response since albumin is synthesized in the liver and has limited value as a measure of nutritional response to substrate administration.[72]

D.2 Impact of complications of cirrhosis on protein turnover

Plasma concentrations of branched chain amino acids are reduced in cirrhosis and this may have a negative impact on skeletal muscle

protein synthesis and breakdown.[72,73] As mentioned earlier, complications of cirrhosis have an adverse impact on skeletal muscle mass and energy metabolism in cirrhosis. Following gastrointestinal bleeding, a large protein load deficient in isoleucine that results in enhanced amino acid oxidation, further reduction in plasma, and muscle amino acid pools contribute to the sarcopenia. This has major clinical implications with the potential use of isoleucine supplementation during gastrointestinal bleeding to prevent worsening muscle mass induced by gastrointestinal bleeding. Other complications including infection and encephalopathy also have the potential to aggravate skeletal muscle proteolysis and impaired protein synthesis in cirrhosis.

D.3 Etiology of cirrhosis and reduced muscle mass

Cirrhosis develops following chronic liver disease due to a number of etiologies that have been recognized to affect skeletal and fat mass. Among cirrhotics, the most severe loss of body protein, muscle area, and function has been reported in those with alcohol related and cholestatic diseases.[74-76] Alcohol has a direct adverse effect on skeletal muscle protein turnover and increased expression of myostatin.[77] Bile salts have been reported to increase muscle oxygen consumption and energy expenditure.[78] Since cirrhosis is a state of accelerated starvation, increased energy expenditure is likely to further impair protein synthesis and accelerate proteolysis**.**

D.4 Molecular mechanisms responsible for sarcopenia of cirrhosis

Data on the skeletal muscle signalling pathways regulating protein synthesis and breakdown have been identified but not studied in cirrhosis.[56] Satellite cell biology has been extensively evaluated and its contributory role in sarcopenia of aging identified.[79] However, there are no studies that have examined the role of impaired satellite cell function in human cirrhotic sarcopenia. A number of reasons contribute to this including the limited interest due to lack of availability of successful therapy, lack of focus on quality of life, and the belief that liver transplantation as a therapeutic advance will correct all the

adverse consequences of cirrhosis. Additionally, the coagulopathy that is almost universal in advanced liver disease has been believed to preclude obtaining muscle biopsies safely. Encephalopathy and ascites limit performing complex and prolonged studies and the heterogeneity of the etiology and stage of the disease are additional factors that have resulted in limited advances in our understanding of the mechanisms of sarcopenia and cachexia in cirrhosis. Finally, given the cross-translational nature of the problem, it is difficult to identify investigators with established expertise in hepatology, metabolism, and molecular and skeletal muscle biology. Notwithstanding these limitations, some advances have been made in this field and lay the foundation for a greater intellectual interaction between hepatologists, developmental biologists, and those with expertise in muscle biology.

The past decade has seen enormous advances in understanding the mechanisms of sarcopenia of aging as well as the regulatory pathways that govern skeletal muscle atrophy, growth, regeneration, and satellite cell function. Discovery of myostatin, a TGFβ superfamily member, and the cross talk between the canonical insulin-like growth factor 1 (IGF1)– Akt–mTOR signalling as well as the ubiquitin proteasome pathways need to be examined in the context of cirrhosis.[55,56] Identification of mTOR regulation by nutrient sensor, AMP kinase, general control of nutrition derepressed (GCN2) as a leucine sensor, and identification of increased skeletal muscle autophagy as a potential contributor to loss of muscle mass as well as its protective role during nutrient starvation are very exciting advances that have not been examined in a disease state.[80-82]

Increased circulating and skeletal muscle expression of myostatin, a TGFβ superfamily member, have been reported in patients with cirrhosis. Myostatin inhibits protein synthesis and increases autophagy. Extensive studies have been performed on myostatin binding to its receptor on the skeletal muscle membrane and the regulation of protein synthesis by inhibition of mTORC1. In contrast, upstream regulation of myostatin is not as well studied, but hyperammonemia has been recognized as an activator of myostatin via an NFKB

mediated mechanism.[83] Hyperammonemia is an activator of reactive oxygen species and this may be another mechanism of activating autophagy. Interestingly, ammonia disposal by the skeletal muscle is mediated via glutamate synthesis in the mitochondria followed by its conversion to glutamine in the cytosol that is transported to the circulation in exchange for leucine that is transported into the muscle. However, within the cell, leucine can either be used for peptide chain elongation or protein synthesis and for activation of mTORC1 by lysosomal transport. An alternate method of leucine metabolism in cirrhosis and potentially hyperammonemia is via mitochondrial oxidation to generate acetyl CoA as a source of energy.

Since the primary mechanism of skeletal muscle ammonia disposal is via cataplerosis (loss of TCA cycle intermediates by enzymatic reactions) of α ketoglutarate (αKG), one option is to increase anaplerosis (addition of 4 and 5 carbon TCA cycle intermediates). This can be achieved by either isoleucine or valine, both of which provide direct anaplerotic input or recent reports that suggest that leucine carbon is used to form αKG. The deamination/ transamination of amino acids as anaplerotic agents results in release of ammonia in a 1:1 stoichiometric ratio with only one net ammonia removed during the formation of glutamine.[84] A novel approach is to provide cell permeable TCA cycle intermediate, αKG that provides the substrate to remove 2 molecules of ammonia in the muscle. A schematic overview of the current concepts in the pathogenesis of sarcopenia and contractile dysfunction in cirrhosis is shown in Figures 1 and 2.[85]

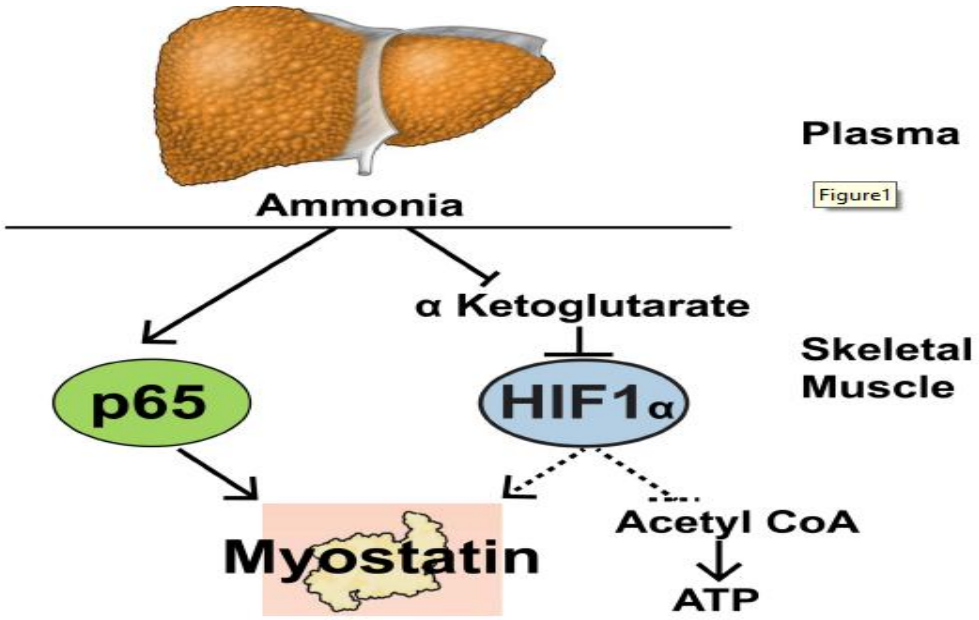


Figure 1: Overview of ammonia induced metabolic and signaling perturbations

Impaired hepatic ureagenesis results in skeletal muscle hyperammonemia. Ammonia transcriptionally upregulates myostatin via a p65NFkB mediated mechanism and decreases α ketoglutarate by cataplerosis. Reduction in α ketoglutarate can stabilize hypoxia inducible factor 1α (HIF1α) that in turn can activate myostatin and inhibit pyruvate to acetyl CoA oxidation (dotted lines are preliminary studies from our laboratory).

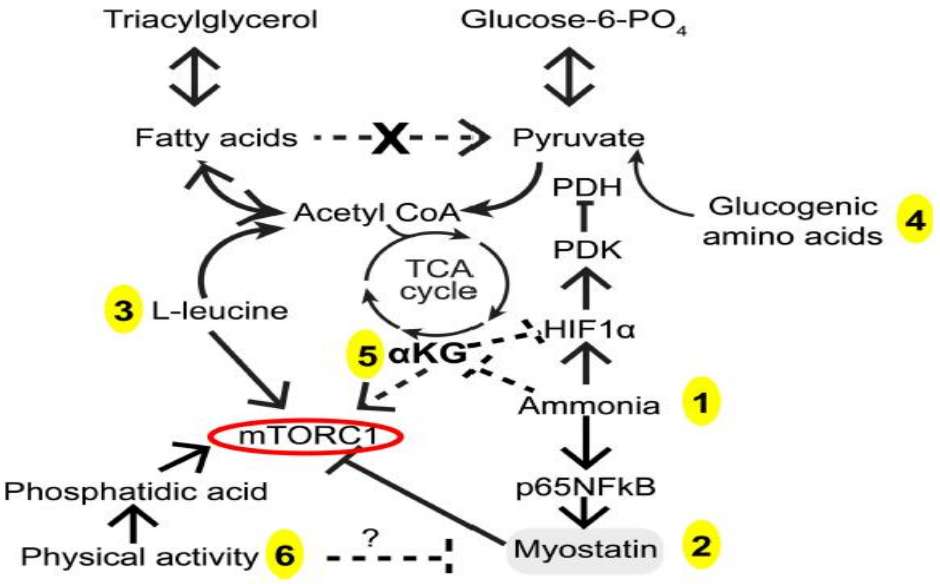


Figure 2: Metabolic abnormalities that contribute to and potential therapeutic targets

Accelerated lipolysis generates acetyl CoA from fatty acids due to impaired pyruvate dehydrogenase (PDH) by hypoxia inducible factor 1α (HIF1α) via pyruvate dehydrogenase kinase (PDK) and possibly directly by ammonia. Cataplerosis of α-ketoglutarate (αKG) by to form glutamate is a metabolic disposal pathway activated in the muscle during hyperammonemia. Lower αKG results in stabilization of HIF1α, decreased mTORC1 activation and decreased tricarboxylic acid (TCA) cycle flux and lower ATP synthesis. These perturbations contribute to lower protein synthesis. Homeostatic responses include the utilization of branched chain amino acids to provide anaplerosis for generate αKG (isoleucine, valine) and acetyl CoA (leucine, isoleucine) with increased transport of branched chain amino acids from circulation for metabolic disposal. Ammonia via a p65NFkB mediated mechanism also activates myostatin that in turn inhibits mTORC1. These metabolic and molecular perturbations contribute to decreased sensitivity to anabolic stimuli (anabolic resistance) that can be potentially reversed by intervention at targeted sites.

Translation of the role of these signalling pathways in liver disease is likely to contribute to identification of potential therapeutic targets that is likely to result in the development of novel therapeutic measures to reverse sarcopenia and cachexia in cirrhosis. In contrast to the sarcopenia of cirrhosis, other systemic disorders and aging are also accompanied by sarcopenia with consequent reduced survival and quality of life .[86-98] The predominant mechanism(s) in these disorders has been an increased proteasome-mediated proteolysis with a lesser contribution from reduced protein synthesis. With aging, there is also a significant contribution of impaired satellite cell function. This has also been shown by us in an animal model with portosystemic shunting but not evaluated in other disease states.

E. Therapeutic options and outcome measures

Therapy for malnutrition in cirrhosis has focused on altering the hormonal and metabolic abnormalities of cirrhosis with very limited success. These have included growth hormone, insulin-like growth factor, testosterone, branched chain amino acid replacement, and late

evening snack.[99-101] Quantifying the effectiveness of therapy requires precise outcome measures. Since skeletal muscle mass and strength have been related to survival and quality of life in cirrhosis as well as other chronic disorders with sarcopenia, studies that focus on such definite measures are necessary.[102,103] Once again, the outcome measures do not focus on reversal of sarcopenia, and limitations of the outcome measures for malnutrition in cirrhosis include the development of ascites and whole body volume overloading, sodium retention, changes in plasma and muscle amino acid concentrations, hyper- and hypo metabolism in over 30% of patients, and the use of lean body mass as a surrogate for skeletal muscle mass. Initial suggestions that low expression of skeletal muscle IGF1 was followed by therapeutic intervention studies using IGF1-IGF1 binding protein complex with limited benefit.[104,105] Recently, we have shown that an increased expression of skeletal muscle myostatin is responsible for reduced muscle protein synthesis and impaired satellite cells in a rat model of portosystemic shunting.[106] We have also shown that the adverse consequences of increased myostatin expression can be reversed without impacting the underlying liver disease which is especially exciting because of the aforementioned data that liver transplantation is not a universally available treatment option and reversing “hepatic cachexia– sarcopenia” can be a major therapeutic option for cirrhosis.

E.1 Nutriceuticals in sarcopenia of cirrhosis

The novel field of nutriceuticals has been shown to be effective in countering sarcopenia of aging.[107] These data have enormous application in patients with cirrhosis and systematic studies with defined outcome measures in reversal of sarcopenia and skeletal muscle function are needed. Use of leucine-enriched essential amino acids to stimulate mTOR independent of upstream inhibitors including myostatin and AMPK has been shown to be effective in other disorders with muscle atrophy.[9] Previous studies on branched amino acid supplementation in patients with cirrhosis have focused on their benefit in encephalopathy with nitrogen balance as a secondary outcome measure (Table 3).[108] It is interesting that the focus of amino acid

supplementation in cirrhosis is based on the lower plasma-branched chain amino acids suggesting that administering these amino acids would result in improvement in outcome. However, since sarcopenia in cirrhosis as in other conditions with anabolic resistance is believed to be due to impaired mTOR signalling response, it can potentially be overcome by leucine-enriched supplementation with amino acids. When branched chain amino acids are administered, stimulation of protein synthesis by leucine is likely to result in increased utilization of other essential amino acids that may then become limiting for protein synthesis. Even though this has not been specifically evaluated in patients with cirrhosis, the alteration in plasma amino acid profile in response to branched chain versus balanced amino acids lends credence to this view.[109] This can be overcome by administering a balanced mixture of essential amino acids with leucine enrichment. Plasma concentrations of aromatic amino acids in cirrhosis are elevated and have been suggested to play a role in the development of hepatic encephalopathy.[72] Therefore, studies to determine the optimum concentration of appropriate amino acid supplementation to derive the maximum skeletal muscle protein response in cirrhotics are necessary. Furthermore, glutamine is a conditionally essential amino acid in cirrhosis and has been shown to directly suppress myostatin expression in muscle cells in vitro.[109] The role of glutamine supplementation in addition to leucine may reverse the molecular abnormalities of increased myostatin and mTOR resistance in cirrhosis to maximize the beneficial effects. Extracellular rather than intracellular concentrations of amino acids have been shown to be potent regulators of muscle protein metabolic response.[110] Therefore, administration of the appropriate combination of essential amino acids to alter plasma concentrations can be an effective therapy in these patients.[110]

The integration of metabolic studies, molecular signalling pathway analyses, and clinically meaningful outcome measures are necessary to have a direct impact on the survival, complications, and quality of life in patients with cirrhosis. Few studies have examined the impact of

interventions on skeletal muscle mass or strength in cirrhotics.[111] This is important because an increase in acute protein synthesis response does not always translate into an increase in muscle anabolism.[112] Finally, the source of dietary proteins, the amino acid composition as well as the digestibility of different proteins and the age of the subject alter the muscle protein metabolic response.[113]

E.2 Role of exercise in cirrhotic patients

The role of aerobic and resistance exercise on skeletal muscle insulin signalling, protein synthesis response, AMP kinase activity, and satellite cell function has been identified.[64] However, fatigue, reduced maximum exercise capacity in cirrhotics, and the presence of complications including ascites, encephalopathy, and portal pressure have limited the translation of the data or the elegant designs of the studies performed in noncirrhotic patients.[114] Resistance exercise increases portal hypertension, and even transient increases in portal hypertension can result in catastrophic variceal bleeding and death.[115] It is therefore critical that the data on the impact of exercise on muscle mass and function be translated very judiciously in cirrhotic patients.

Novel strategies to reverse cachexia including myostatin antagonists are also of clinical interest especially given recent data that myostatin may play a critical role in cirrhotic sarcopenia.[116] Given the paucity of data, the understudied nature of the problem, sarcopenia in cirrhosis deserves to be recognized as an area of unmet need with the potential to improve the outcome of the large number of patients with cirrhosis. One potential strategy for development of novel and successful therapies is the need for consilience between the diverse and seemingly unrelated fields identified earlier. A putative therapeutic approach to sarcopenia in cirrhosis is suggested in Fig. 3.

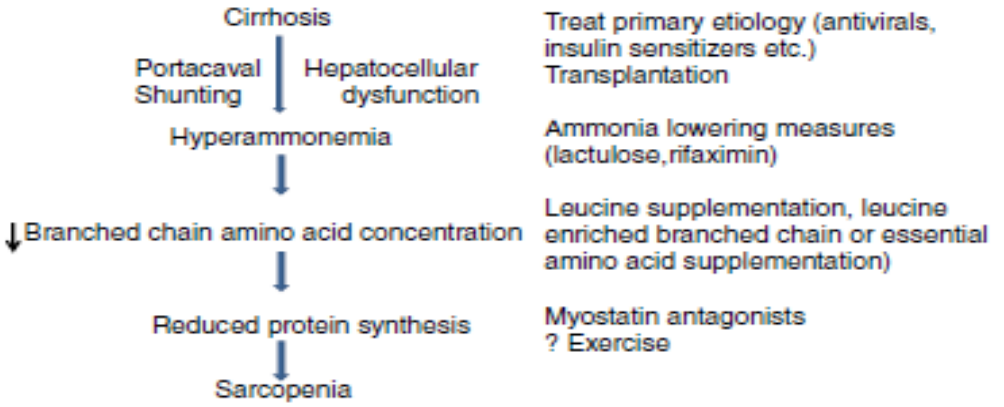


Figure 3: Potential mechanism of sarcopenia

Assessment of sarcopenia

Sarcopenia is generally defined as a reduction in muscle mass two standard deviations below the healthy young adult mean.[117] Sarcopenia is traditionally associated with aging; however, it can occur earlier in patients with malignancy and chronic disease.[118] Despite the recent consensus statement of the European Working Group on Sarcopenia in Older People that recommends taking into account both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia,[119] the use of muscle mass vs function to define sarcopenia remains controversial. Moreover, muscle mass alone has been widely used to define sarcopenia and is associated with prognosis in patients with various conditions.[119] As CT or MRI imaging is the gold standard tool to quantify skeletal muscle mass, skeletal muscle mass calculated from abdominal cross-sectional images is a great resource to define sarcopenia.

Sarcopenia has garnered increasing interest among clinicians over recent decades and is now classed as a geriatric syndrome; the current definition is age-associated loss of skeletal muscle mass as well as diminished muscle strength and/or physical performance, which is associated with reduced physical capability, impaired cardiopulmonary performance, disability, and mortality among older people.[120] Skeletal muscle area derived from a single slice CT has become more easily reproducible, and reduces the radiation exposure required to only 2.6 millisieverts. Measuring cross-sectional muscle area at either the level

of the third (L3) or fourth (L4) lumbar vertebrae has been shown to correlate well with total body muscle mass (r = 0.71), and it is now accepted as a safe and accurate means of estimating muscle mass. When adjusted for patient height to take stature into account it is referred to as skeletal muscle index (SMI will be calculated of Slice-O-matic software, version 4.3 (Tomovision), Montreal, QC, Canada).**).**L3 skeletal muscle index has been shown to be of higher accuracy in the diagnosis of sarcopenia in cirrhosis than anthropometry or DEXA scanning and is now the most commonly employed method in studies investigating sarcopenia in cirrhosis. Diagnostic criteria have been extrapolated from Cirrhosis populations.[121] Multiple studies in cirrhosis which have employed this definition have produced clinically meaningful results and it is increasingly accepted as the most appropriate definition of sarcopenia when using cross-sectional imaging. Muscle strength was assessed by grip strength and measured using a dynamometer. The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand to make sure that the middle phalanx rested on the inner handle. The participant was allowed to perform one test trial. After this, three trials followed and the best score was used for analysis. Handgrip strength was expressed in kilogrammes (Kg).[121] Three trials for each hand were carried out and we used the highest value for diagnosing sarcopenia. Low handgrip strength was defined as <26 kg in men and <18 kg in women.[122] Usual gait speed (m/s) on a 4 meter course was used as an objective measure of physical performance and a slow walking speed was defined as a walking speed less than 0.8 m/s.

Normative values of these indices in Indian population, three thousand eighty-seven number of patients, 1003 (32%) females and 2084 (67%) males who underwent abdominal CT were enrolled in this study. Mean CTSI in female was 41.25±4.42 vs. 44.33±6.56 in male (p<0.0001). Mean of HGS in female was 25.19±7.57 vs. 35.14±8.56 in male

(p<0.0001), mean of gait velocity in female was 1.23±0.31 vs. 1.25±0.30 in male (p=0.2524).

Table 3: Variables for assessment of sarcopenia

Variable	Clinical practice	Research studies
Skeletal muscle Strength	Grip strength Chair stand test (chair rise test)	Grip strength Chair stand test (5-times sit-to-stand)
Skeletal muscle mass or Skeletal muscle quality	Appendicular skeletal muscle mass (ASMM) by Dual-energy X-ray absorptiometry (DXA)* Whole-body skeletal muscle mass (SMM) or ASMM predicted by Bioelectrical impedance analysis (BIA)* Lumbar muscle cross-sectional area by CT or MRI	ASMM by DXA Whole-body SMM or ASMM by Magnetic Resonance Imaging (MRI, total body protocol) Lumbar muscle cross-sectional area by CT or MRI Muscle quality by mid-thigh or total body muscle quality by muscle biopsy, CT, MRI or Magnetic resonance Spectroscopy (MRS)
Physical Performance	Gait speed Short physical performance battery (SPPB) Timed-up-and-go test (TUG) 400-meter walk or long-distance corridor walk (400-m walk)	Gait Speed SPPB TUG 400-m walk

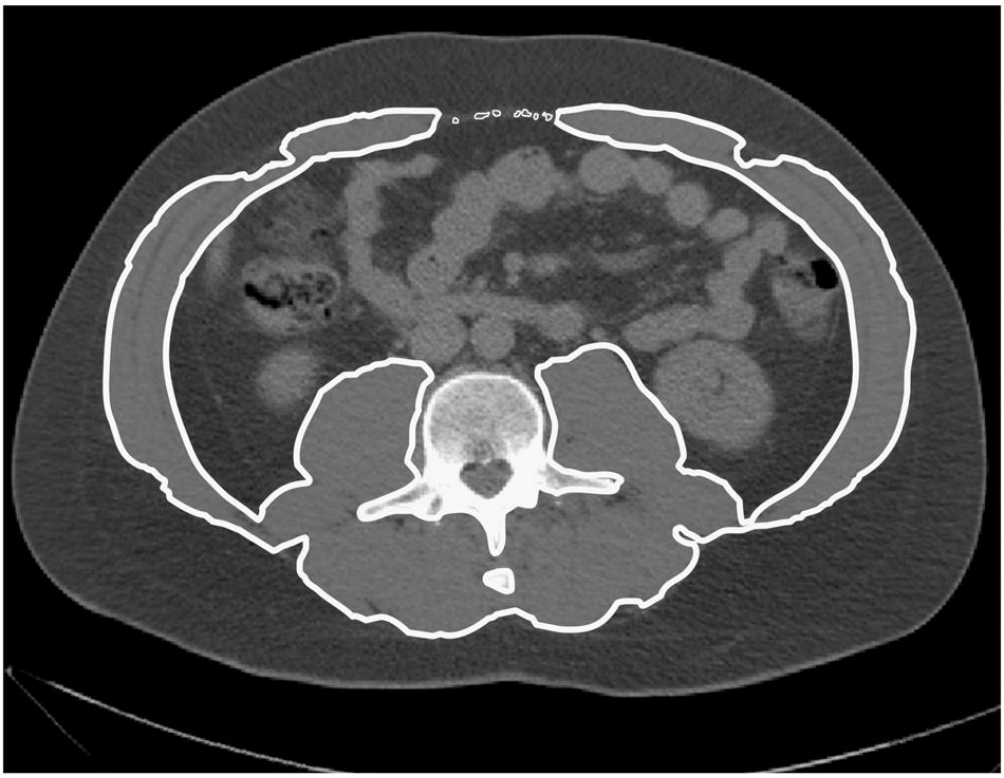


Figure 4: Example of a CT slice at the level of the third lumbar vertebra on which muscle was analyzed of the selected muscle, area can be computed, to determine skeletal muscle area (SMA)

MATERIALS AND METHODS

Source of Data

The study was conducted on patients of Liver Cirrhosis admitted in the Inpatient Department of Gastroenterology units of Dayanand Medical College and Hospital, Ludhiana. The subjects were enrolled in a duration of April 2018 to November 2018 with cirrhosis and a follow up of six months.

METHOD OF COLLECTION OF DATA

The Investigator completed a full medical record regarding the cirrhosis, its etiology, complications and co morbidities. The severity of cirrhosis was assessed using the Child-Pugh score and the MELD score; Furthermore, patients participated in the following procedures:

- **Muscle mass:**

  L3 skeletal muscle index calculation (Slice-O-matic software, version 4.3 (Tomovision), Montreal, QC, Canada)

- **Muscle strength :Handgrip strength measurement:**

  Muscle strength was assessed by grip strength and measured using a dynamometer. The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand to make sure that the middle phalanx rested on the inner handle. The participant was allowed to perform one test trial. After this, three trials followed and the best score was used for analysis. Handgrip strength was expressed in kilogrammes (Kg).

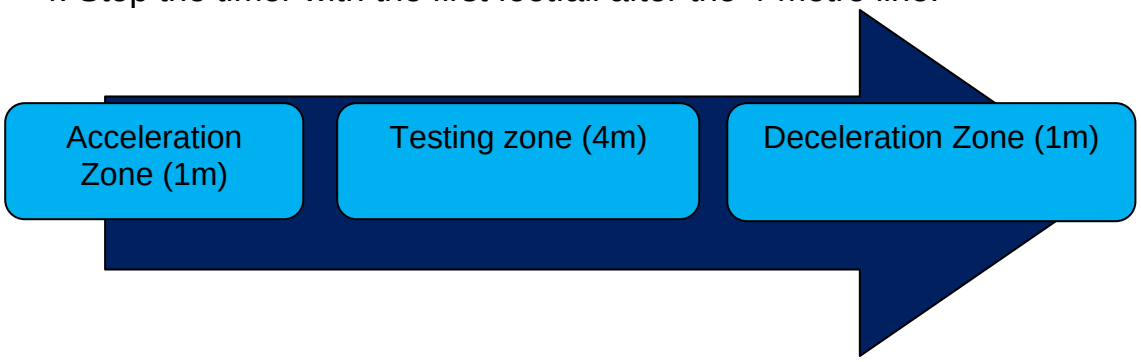
- **Muscle performance status:**

  For measurement of muscle performance status gait velocity was measured. Gait velocity was measured according to the following protocol:

Gait Speed Test (4-metre): Instructions:

The test was done with any patient able to walk 4 metres using the instructions below:

1. Patient was instructed to walk at their normal pace. Patients could use an assistive device, if needed.
2. Patient was asked to walk down a hallway through a 1-metre zone for acceleration, a central 4-metre “testing” zone, and a 1-metre zone for deceleration (the patient should not start to slow down before the 4-metre mark).
3. Start the timer with the first footfall after the 0-metre line.
4. Stop the timer with the first footfall after the 4-metre line.



Six months after the baseline assessment of the study samples, data was collected regarding survival through telephonic cummunications and follow up visits if any.

Clinical and laboratory Assessment

Baseline Clinical and blood biochemical data, will be obtained. Liver Function test, Renal function test, PTI/INR will be recorded.

Inclusion Criteria:

Adults with cirrhosis.

Exclusion Criteria:

- Patients with advanced stages of hepatocellular carcinoma
- Patient not giving consent
- In hepatic coma, with acquired immunodeficiency syndrome
- Pancreatic insufficiency
- Receiving enteral nutrition
- Pregnancy and lactation

Duration of study- The subjects were enrolled from February 2018 to November 2018 with a follow up of 6 months.

OUTCOMES

Primary Outcome: Survival at 6 months

Secondary Outcome

- Variceal bleed
- Ascites: Denovo or diuretic responsive or Refractory
- Overt Hepatic Encephalopathy
- Sepsis

STATISTICAL ANALYSIS

Continuous variables expressed as median (range). The Mann–Whitney U test was used to evaluate the significance of differences in median values. The chi-square test or Fisher's exact test was used to compare differences in categorical variables between groups. All analyses were carried out using SPSS version 21 software. $P < 0.05$ was considered statistically significant.

OBSERVATIONS AND RESULTS

DISTRIBUTION OF ETIOLOGY OF CIRRHOSIS IN THE STUDY POPULATION

Table 4: Shows distribution of study of cirrhosis in study population

		Sex				Total	Chi-square value	p-value
		Female		Male				
Etiology	Alcohol	2	5%	98	81%	100	89.224	0.000
	Alcohol and HCV	0	0%	1	1%	1		
	Autouimmune	1	3%	0	0%	1		
	HBV	0	0%	1	1%	1		
	HCV	6	15%	10	8%	16		
	HCV and HCC	0	0%	1	1%	1		
	NASH	31	78%	10	8%	41		
Total		40	100%	121	100%	161		

The following table no 4 and figure no 5 show that the most common etiological factor responsible for causing cirrhosis in our study population was alcohol with 81(61%) patients out of 131 due to alcohol. NASH related cirrhosis was the most common cause after alcohol as an etiological factor for cirrhosis with 38(29%) out of 131 due to it.

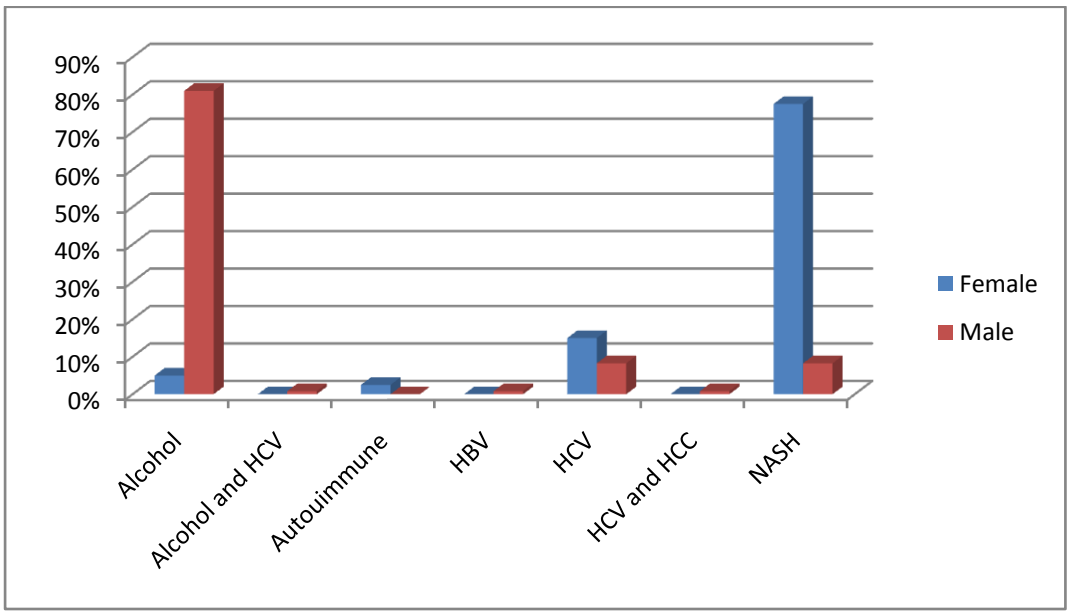


Figure 5: Shows distribution of etiology of cirrhosis in study population

DISTRIBUTION OF HEIGHT WEIGHT AND BMI IN TOTAL STUDY POPULATION

Table 5: Shows distribution of height, weight and BMI in study population

	Female		Male		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Height	160.28	8.85	170.45	28.70	-2.203	0.029	-19.29	-1.05
Weight	62.63	8.83	69.00	12.30	-3.022	0.003	-10.53	-2.20
BMI	24.71	5.42	24.10	5.25	0.625	0.533	-1.30	2.51

Above table shows there was signigicant difference in height and weight amongst gender but not in BMI with a p value <0.05. the following figure also depicts the same.

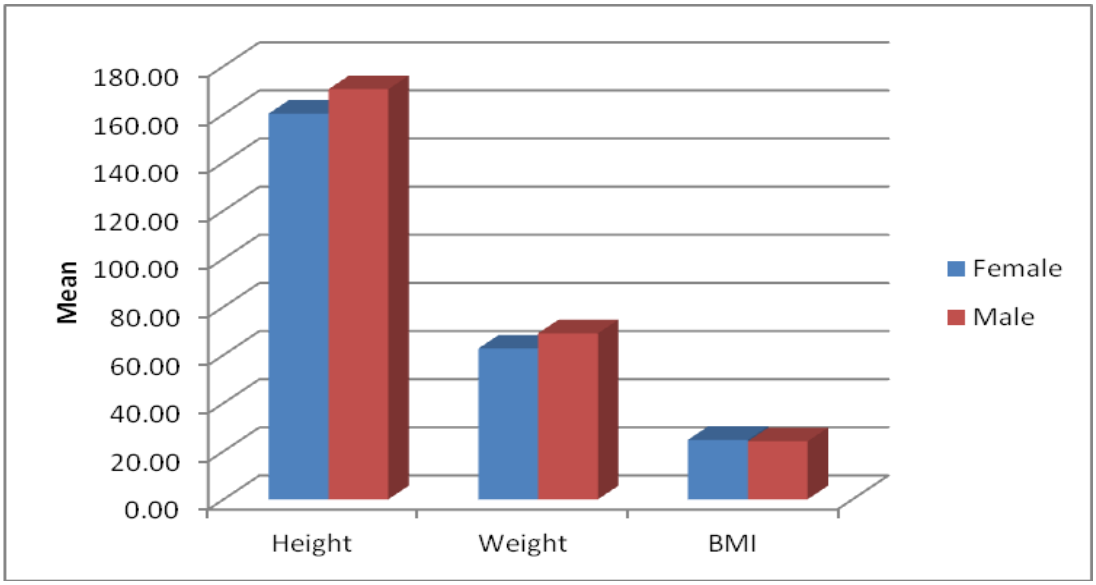


Figure 6: Shows distribution of height weight and BMI in study population

DISTRIBUTION OF CTP SCORE WITH MELD SCORE IN STUDY POPULATION

Table 6: Distribution of CTP and MELD score in study population

	Female		Male		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
CTP score	9.58	1.69	10.47	2.19	-2.362	0.019	-1.65	-0.15
MELD score	21.40	6.30	21.70	7.98	-0.218	0.828	-3.04	2.43

Above table shows that there is a significant difference in the baseline CTP score in both sexes with a p value of 0.019. On the contrary there was not much significance in the baseline MELD score with a p value of 0.82 which can be explained as there was not much significant difference in the baseline laboratory parameters amongst the both sexes

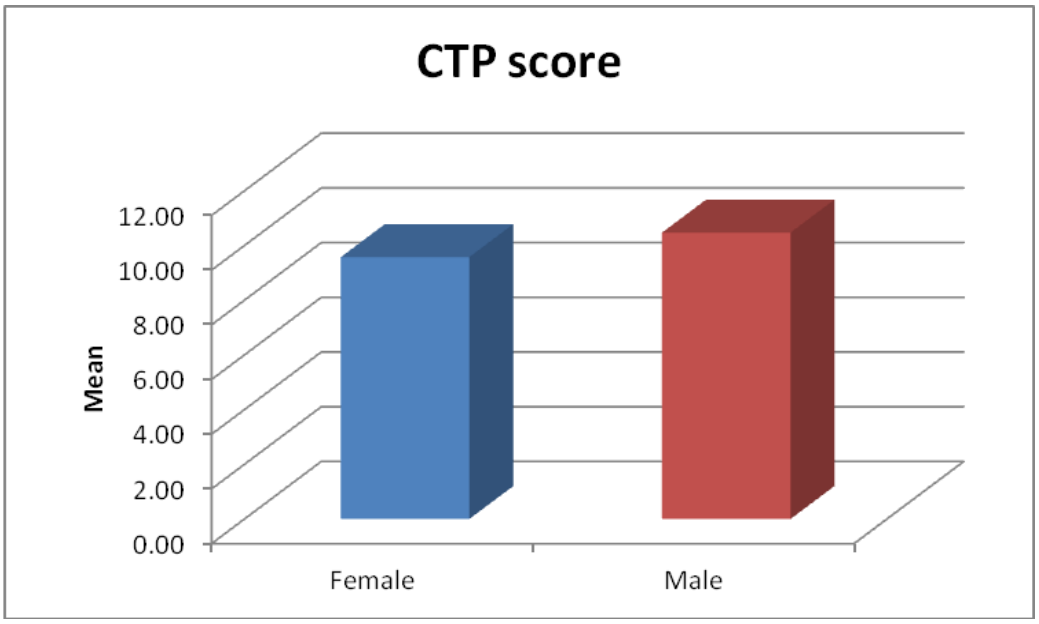


Figure 7A: Distribution of CTP score in both sexes

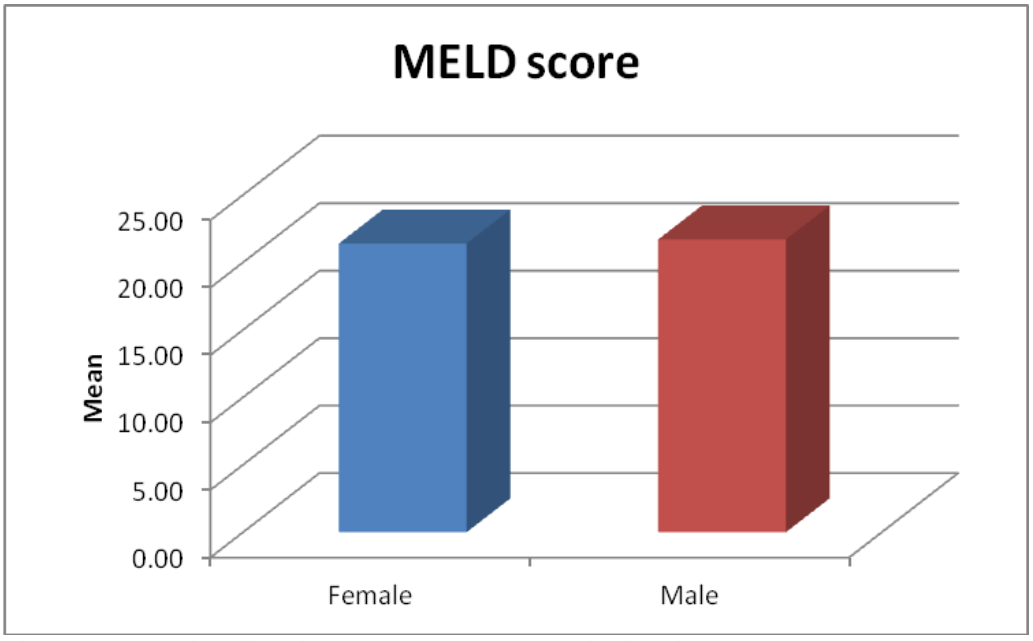


Figure 7B: Distribution of MELD score in both sexes

PREVALENCE OF SARCOPENIA

Table 7: Shows the prevalence of sarcopenia in patients with cirrhosis

SACRO	No. of cases	Percentage
N	30	19%
Y	131	81%
Total	161	100%

There is 81% prevalence of sarcopenia in patients with cirrhosis. Following is also a pie chart showing the proportion of patients with sarcopenia in the whole study population.

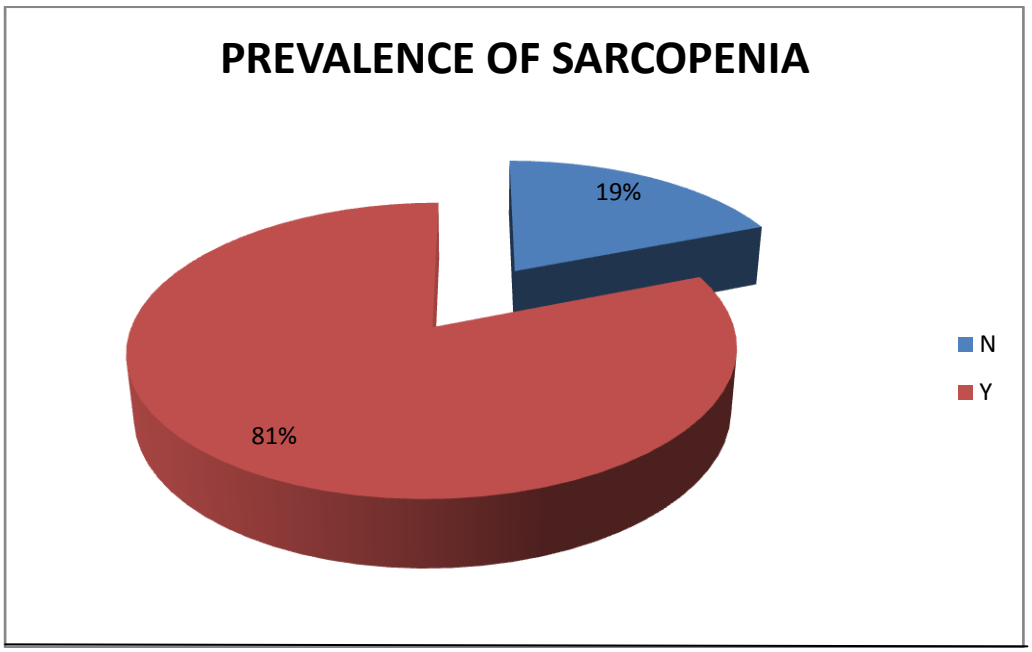


Figure 8: Shows the proportion of patients with sarcopenia out of whole study population

SURVIVAL IN PATIENTS WITH SARCOPENIA

Table 8: Shows survival in patients with sarcopenia

		Outcome				Total	Chi-square value	p-value
		Survival		Expired				
SARCOPENIA	N	18	60%	12	40%	30	0.040	0.842
	Y	76	58%	55	42%	131		
Total		94	58%	67	42%	161		

There is significant difference in survival in patients of liver cirrhosis with or without sarcopenia. Following is a bar diagram to show that there were more deaths in patients with sarcopenia.

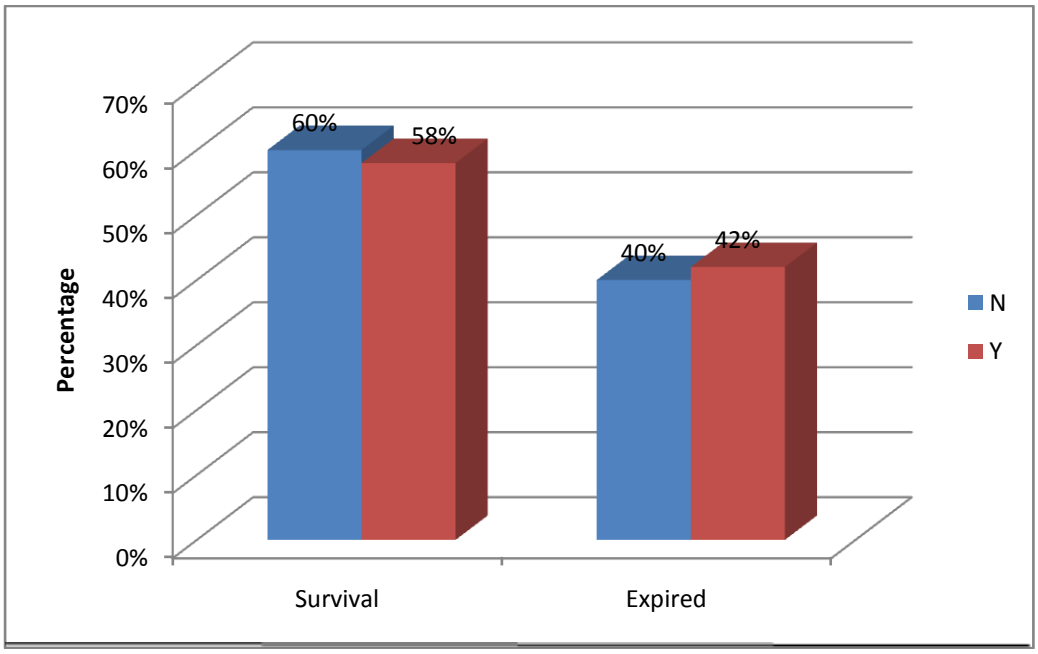


Figure 9: Survival in patients of cirrhosis with sarcopenia

SURVIVAL IN PATIENTS WITH SARCOPENIA IN MALES AND FEMALES IN THE STUDY POPULATION

Table 9: Shows survival in patients of sarcopenia with cirrhosis

		outcome				Total	Chi-square value	p-value
		Survival		Expired				
Sex	F	33	43%	3	5%	36	23.544	0.000
	M	43	57%	52	95%	94		
Total		76	100%	55	100%	131		

Of the 131 patients with sarcopenia there was significant difference in the survival in males and female at 6 months with survival being more in females. More proportion of females with sarcopenia survived as compared to males.

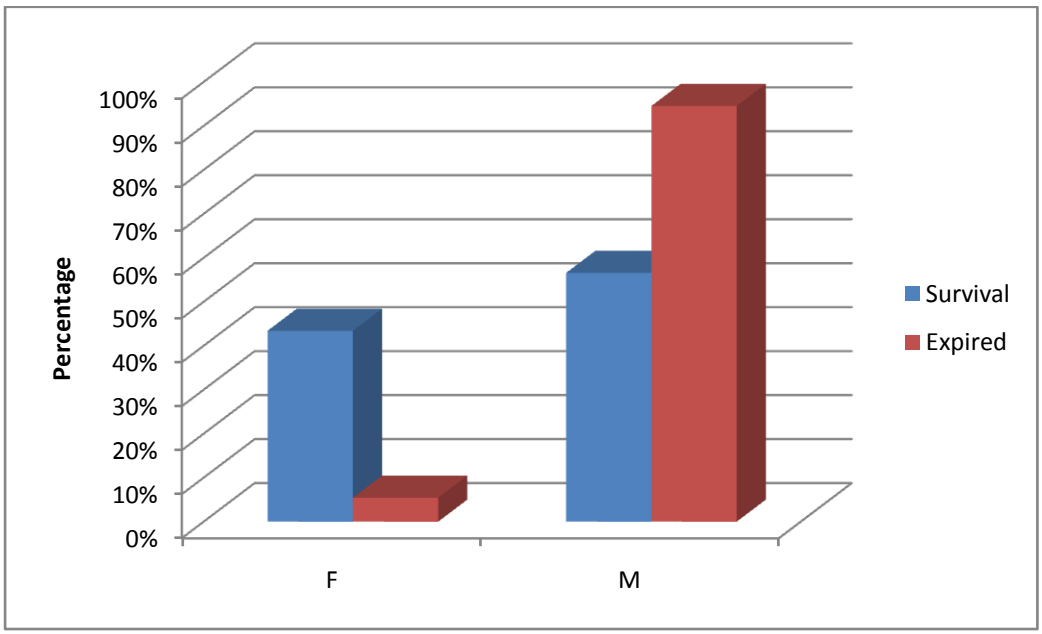


Figure 10: Shows survival in males and females

SURVIVAL IN SARCOPENIC PATIENTS WITH ASCITES

Table 10: Shows distribution of ascites with relation to survival in patients of sarcopenia with cirrhosis

		outcome				Total	Chi-square value	p-value
		Survival		Expired				
ASCITES (BASE)	NO	21	28%	18	33%	39	0.9396	0.529
	YES	55	72%	37	67%	92		
Total		76	100%	55	100%	131		

There was no significant difference in patients of cirrhosis with sacopenia in relation to the presence of ascites for survival at 6 months.

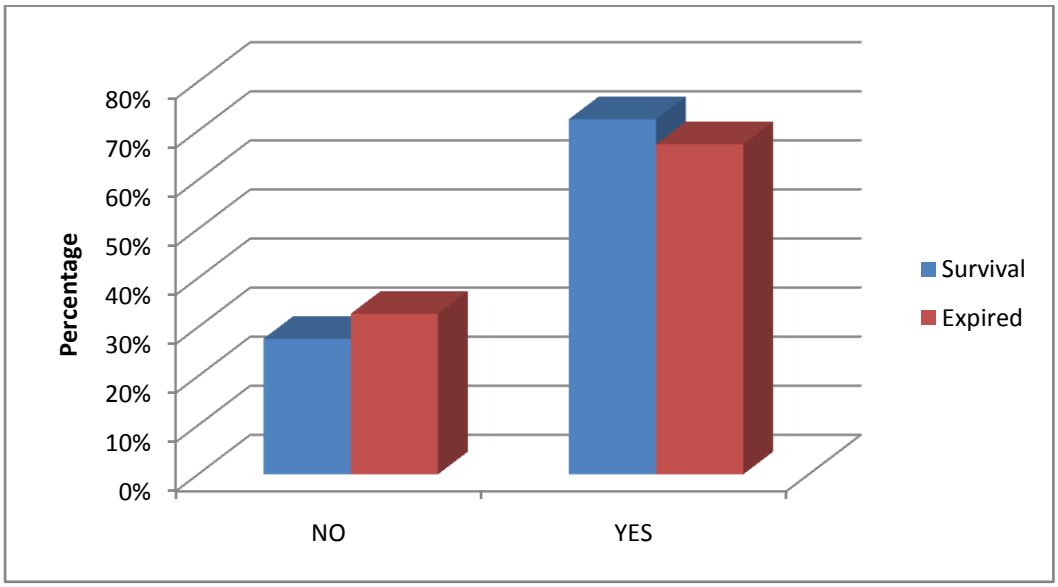


Figure 11: Shows presence or absence of ascites with relation to survival in patients of cirrhosis with sarcopenia

SURVIVAL IN SARCOPENIC PATIENTS WITH BLEEDING

Table 11: Shows presence or absence of bleeding in patients of cirrhosis with sarcopenia

		outcome				Total	Chi-square value	p-value
		Survival		Expired				
Upper GI bleed	NO	74	97%	48	87%	122	5.083	0.024
	YES	2	3%	7	13%	9		
Total		76	100%	55	100%	131		

Patients of cirrhosis with sarcopenia in the presence of UGI bleed had lower survival as shown in the table no 11 and in figure no 12.

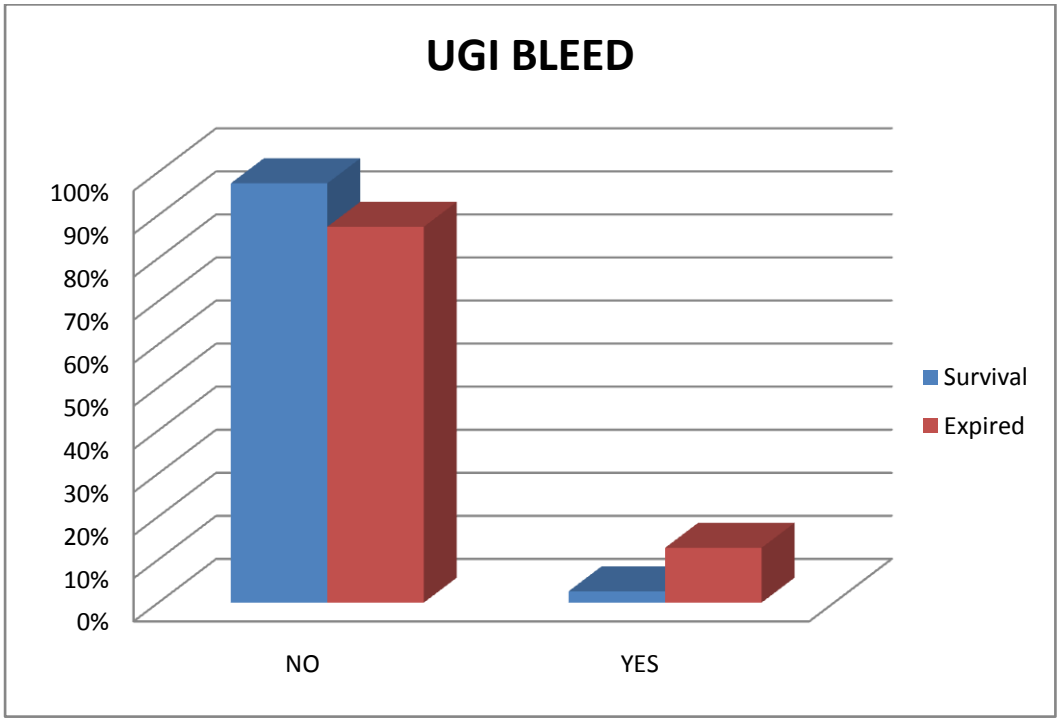


Figure 12: Shows relation of survival in patients with bleeding in patients of cirrhosis with sarcopenia

SURVIVAL IN SARCOPENIC PATIENTS WITH HEPATIC ENCEPHALOPATHY

Table 12: Shows presence or absence of hepatic encephalopathy in patients of cirrhosis with sarcopenia

		outcome				Total	Chi-square value	p-value
		Survival		Expired				
HE	NO	69	91%	40	73%	109	7.499	0.006
	YES	7	9%	15	27%	22		
Total		76	100%	55	100%	131		

Patients of cirrhosis with sarcopenia in the presence of Hepatic Encephalopathy had lower survival as shown in the table no 12 and in figure no 13.

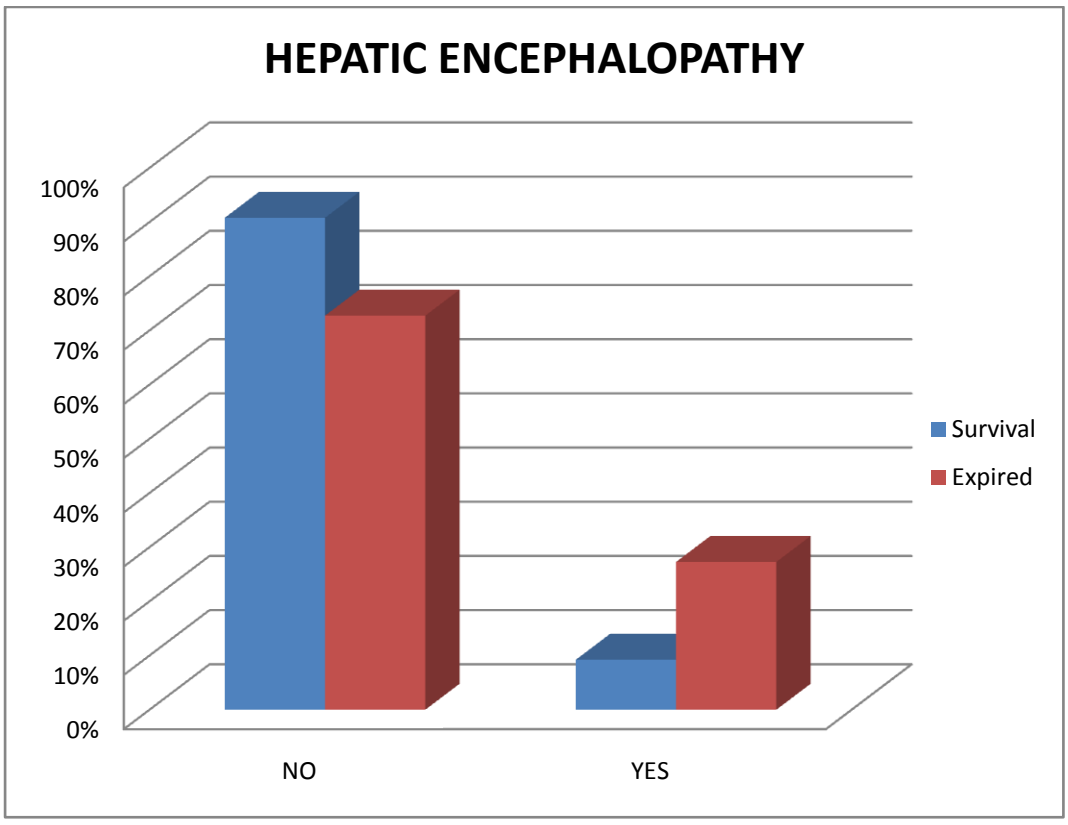


Figure 13: Shows relation of survival in patients with hepatic encephalopathy in patients of cirrhosis with sarcopenia

CORRELATION WITH SURVIVAL WITH ETIOLOGY OF CIRRHOSIS

Table 13: Shows distribution of etiology of cirrhosis in patients of liver cirrhosis with sarcopenia

		outcome				Total	Chi-square value	p-value
		Survival		Expired				
Etiology	Alcohol	35	46%	45	82%	80	25.029	0.000
	Alcohol and HCV	0	0%	1	2%	1		
	HCV	7	9%	4	7%	11		
	HCV and HCC	0	0%	1	2%	1		
	NASH	34	45%	4	7%	38		
Total		76	100%	55	100%	131		

Following figure and above table show correlation of survival with etiology of cirrhosis in patients with sarcopenia with the alcohol being most common etiology of cirrhosis. Worst survival was seen with alcohol related cirrhosis with a significant difference with other etiologies.

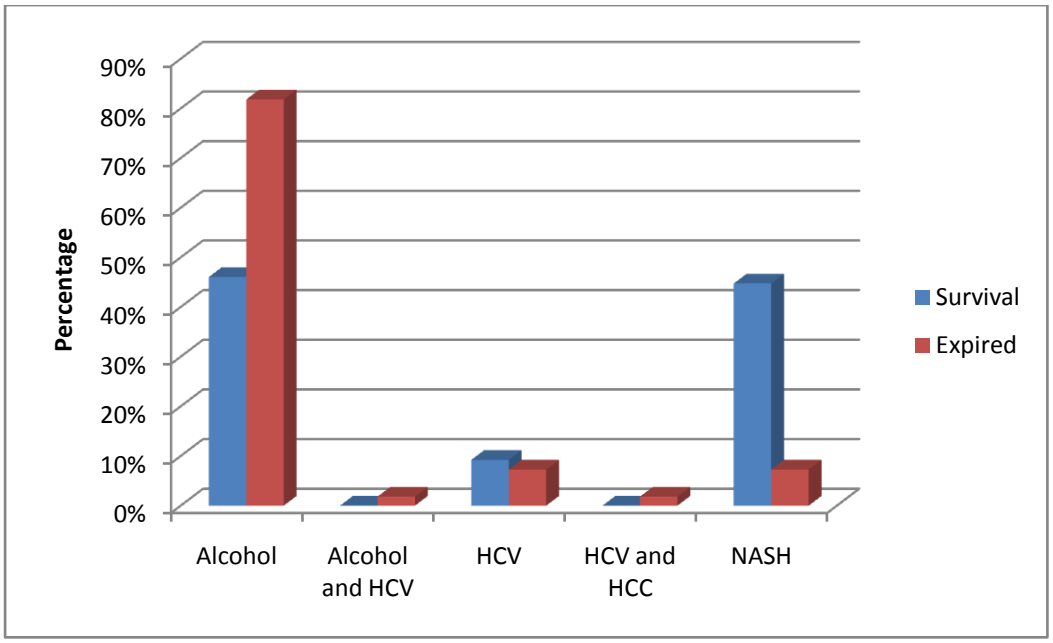


Figure 14: Shows distribution of etiology of cirrhosis in patients of liver cirrhosis with sarcopenia

CORRELATION OF HEIGHT, WEIGHT AND BMI IN THE STUDY POPULATION WITH SURVIVAL IN SARCOPENIC CIRRHOSIS PATIENTS

Table 14: Correlation of height weight and BMI in patients of cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Height	164.23	8.65	173.84	41.89	-1.945	0.054	-19.38	0.17
Weight	65.11	11.35	72.42	12.33	-3.492	0.001	-11.45	-3.17
BMI	24.32	5.13	24.74	6.39	-0.413	0.680	-2.41	1.58

Patients with less weight had longer survival

No difference was observed in height and BMI of the study population.

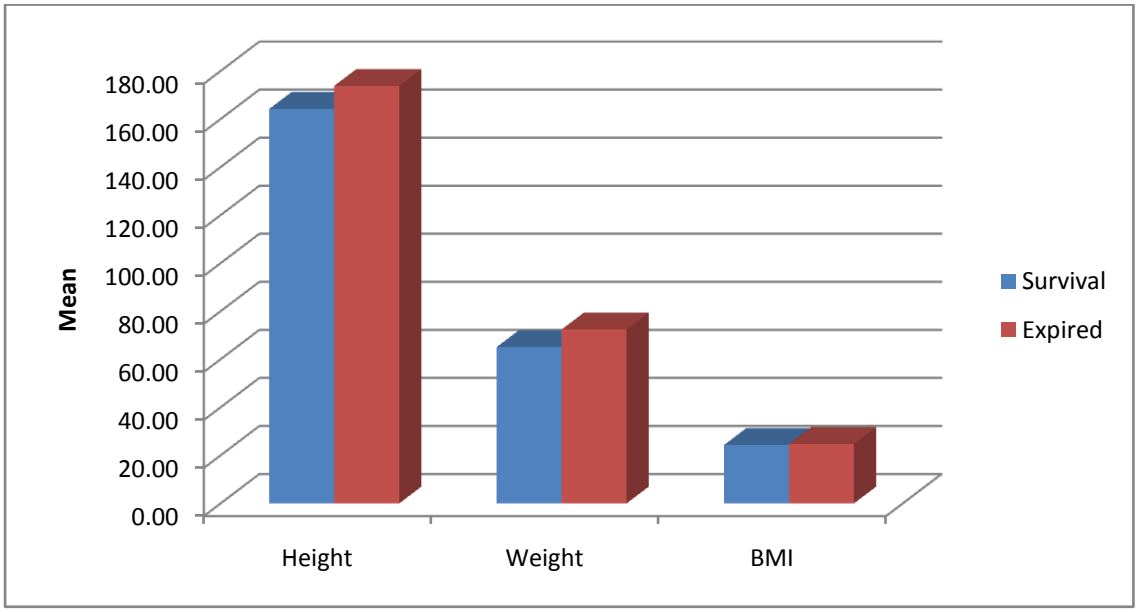


Figure 15: Bar diagram showing correlation of height, weight and BMI with survival in study population

CORRELATION OF HAEMOGLOBIN, TOTAL LEUKOCYTE COUNT, SODIUM LEVELS AT BASELINE WITH SURVIVAL

Table 15: Correlation of haemoglobin TLC and sodium levels at baseline with survival in patients of cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
HB baseline	9.67	2.42	9.78	2.82	-0.220	0.826	-1.09	0.88
TLC Baseline	11.57	7.08	11.80	7.75	-0.159	0.874	-3.02	2.57
NA+	132.04	7.21	132.77	6.04	-0.566	0.573	-3.30	1.83

There was no correlation in sarcopenic patients with survival at 6 months with respect to their haemoglobin and total leukocyte count at baseline.

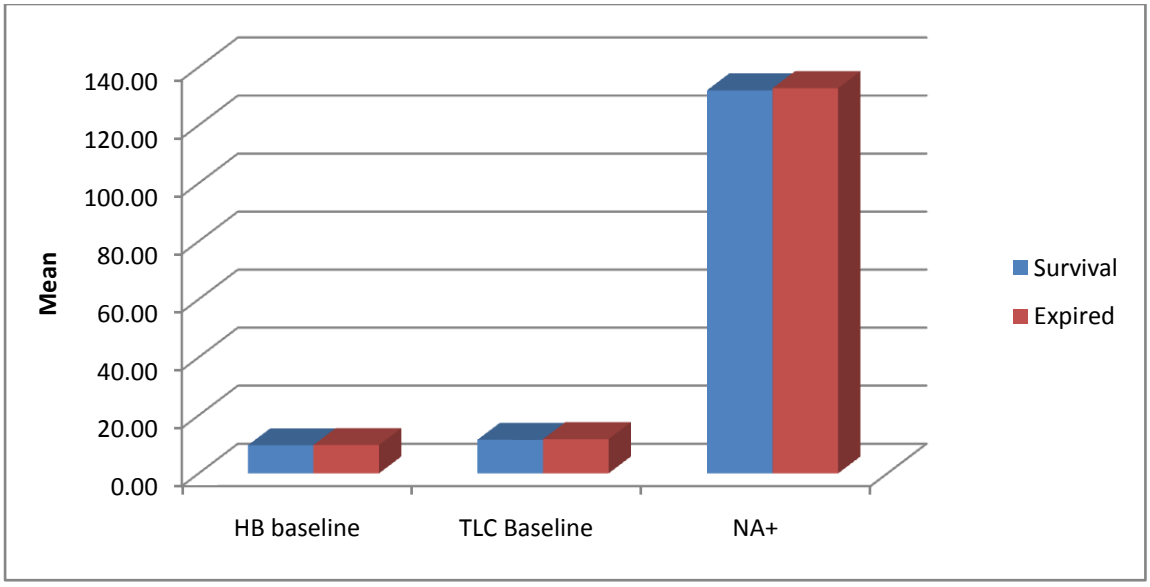


Figure 16: Correlation of survival of haemoglobin TLC sodium levels at baseline with survival

CORRELATION OF PTI-INR, BILIRUBIN (T), AND ALBUMIN AT BASELINE WITH SURVIVAL IN PATIENTS WITH CIRRHOSIS WITH SARCOPENIA

Table 16: Correlation of survival of PTI-INR, Bilirubin (T), and albumin levels at baseline in patients of cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
INR	1.43	0.78	1.41	0.34	0.161	0.873	-0.21	0.24
Bilirubin T baseline	6.75	7.44	8.28	9.10	-1.038	0.301	-4.43	1.38
Albumin Baseline	2.67	0.62	2.68	0.48	-0.098	0.922	-0.21	0.19

There was no correlation of bilirubin (T), PTI-INR, and albumin levels at baseline in the patients with sarcopenia with survival at 6 months.

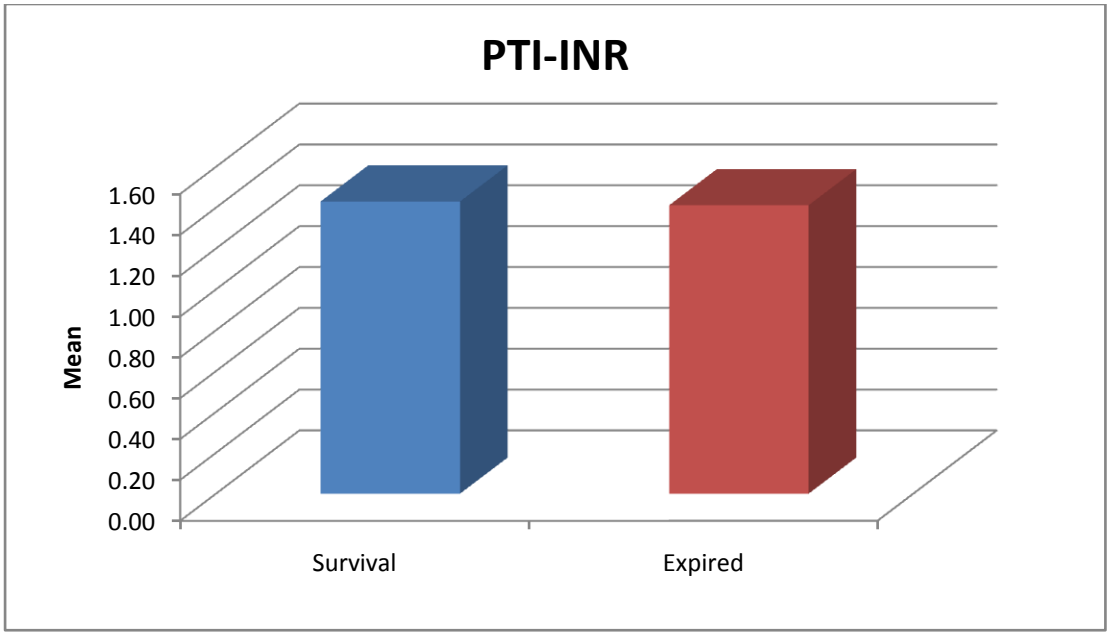


Figure 17A: Correlation of survival with INR levels at baseline

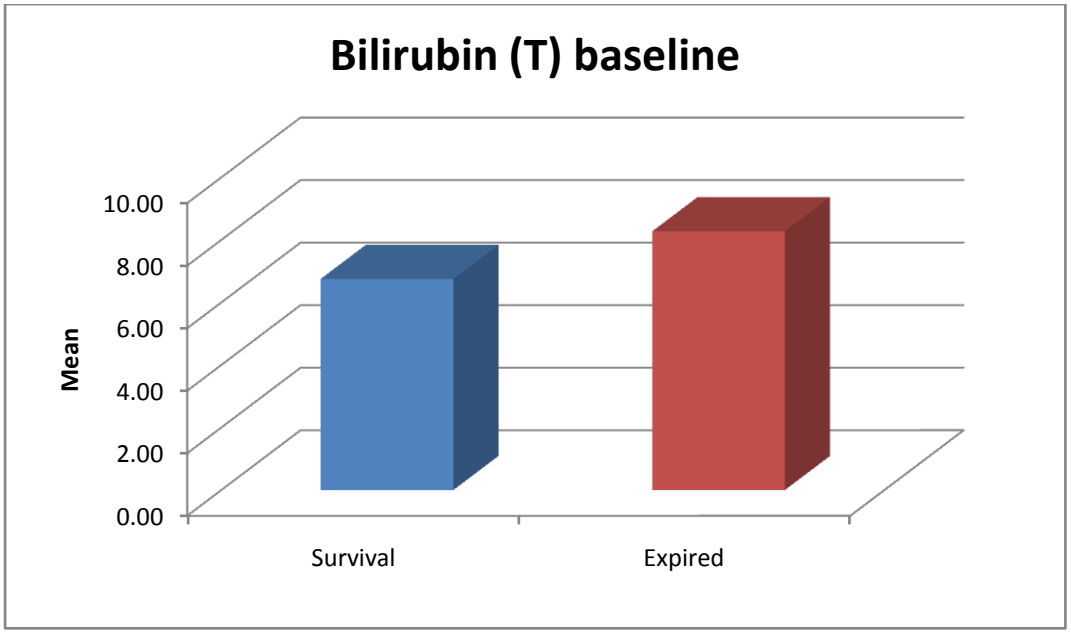


Figure 17B: Correlation of survival with Bilirubin (T) levels at baseline

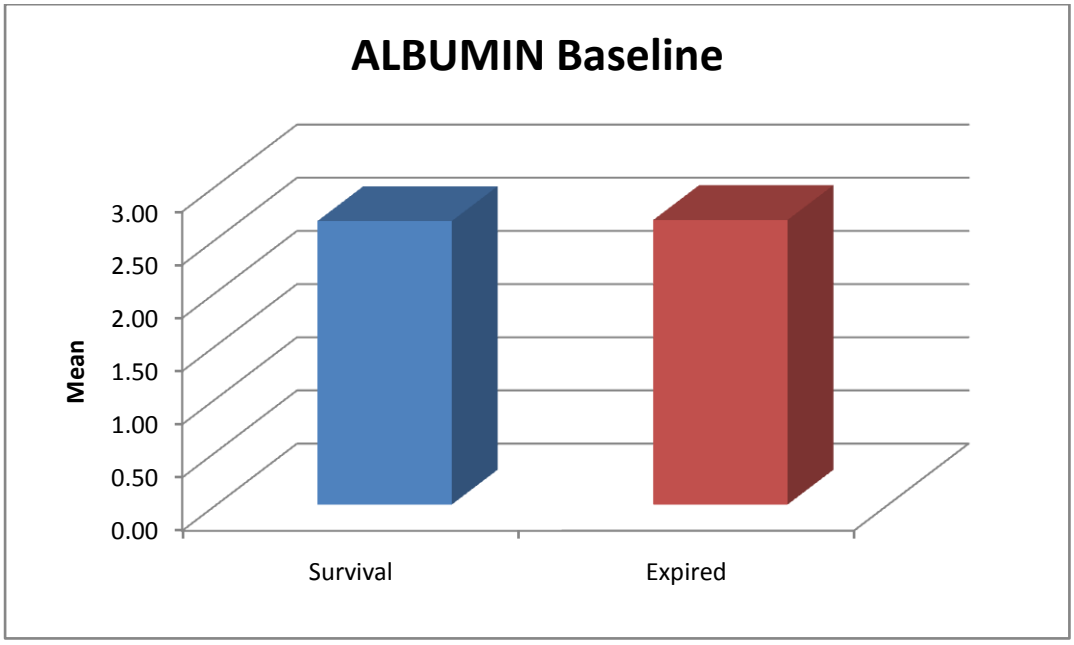


Figure 17C: Correlation of survival with Albumin levels at baseline

CORRELATION OF LEVELS OF CREATININE WITH SURVIVAL IN PATIENTS WITH SARCOPENIA

Table 17: Correlation of creatinine levels with survival in patients of cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Creatinine	1.09	1.21	1.30	0.72	-1.111	0.269	-0.58	0.16

There was no difference in creatinine levels in survivors and non survivors

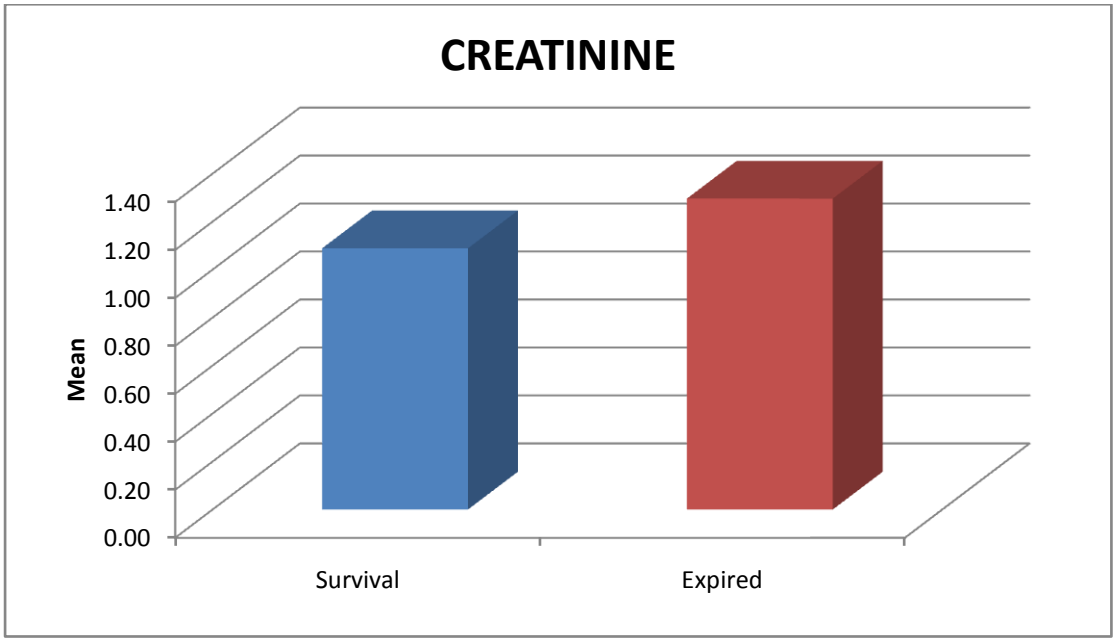


Figure 18: Correlation of creatinine levels with survival

CORRELATION OF GAIT VELOCITY IN PATIENTS OF SARCOPENIC CIRRHOSIS WITH SURVIVAL

Table 18: Correlation of gait velocity with survival in patients of liver cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Gait velocity	0.66	0.20	0.53	0.15	8.456	0.000	-1.09	-0.68

Significant correlation was found in patients of cirrhosis with sarcopenia in reference to gait velocity. Gait velocity was faster in survivors as compared to non survivors.

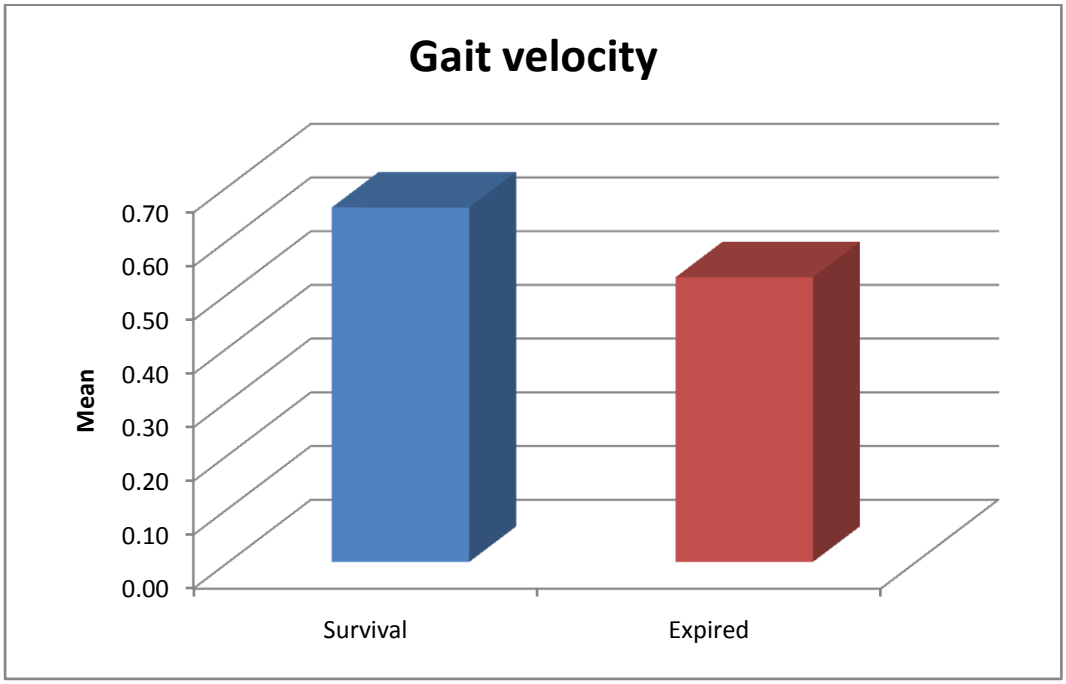


Figure 19: Correlation of gait velocity with survival

CORRELATION OF HAND GRIP STRENGTH AND L3SMI WITH SURVIVAL IN SARCOPENIC PATIENTS

Table 19: Correlation of hand grip strength and L3SMI levels with survival in patients of liver cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Hand Grip strength	20.24	7.88	15.01	6.84	3.931	0.000	2.59	7.85
Skeletal muscle index level	28.06	6.55	28.12	6.59	-0.051	0.960	-2.37	2.25

There was significant correlation of hand grip strength with survival. Patients who died had lower hand grip strength.

No significant difference was observed in patients with respect to L3SMI levels for survival at six months (pvalue-0.960).

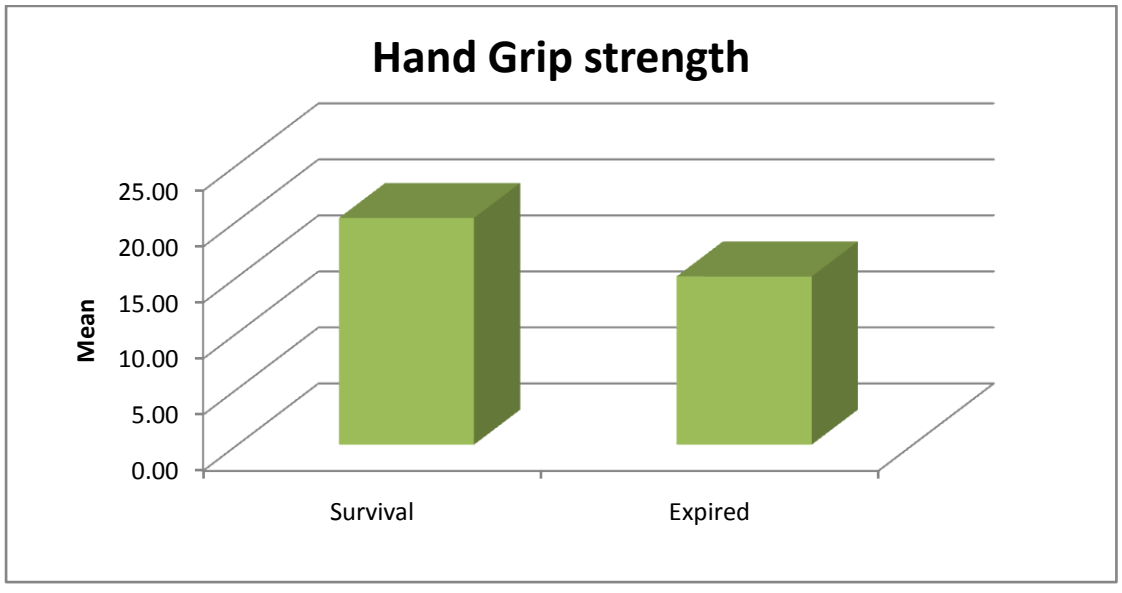


Figure 20A: Correlation of survival with hand grip strength

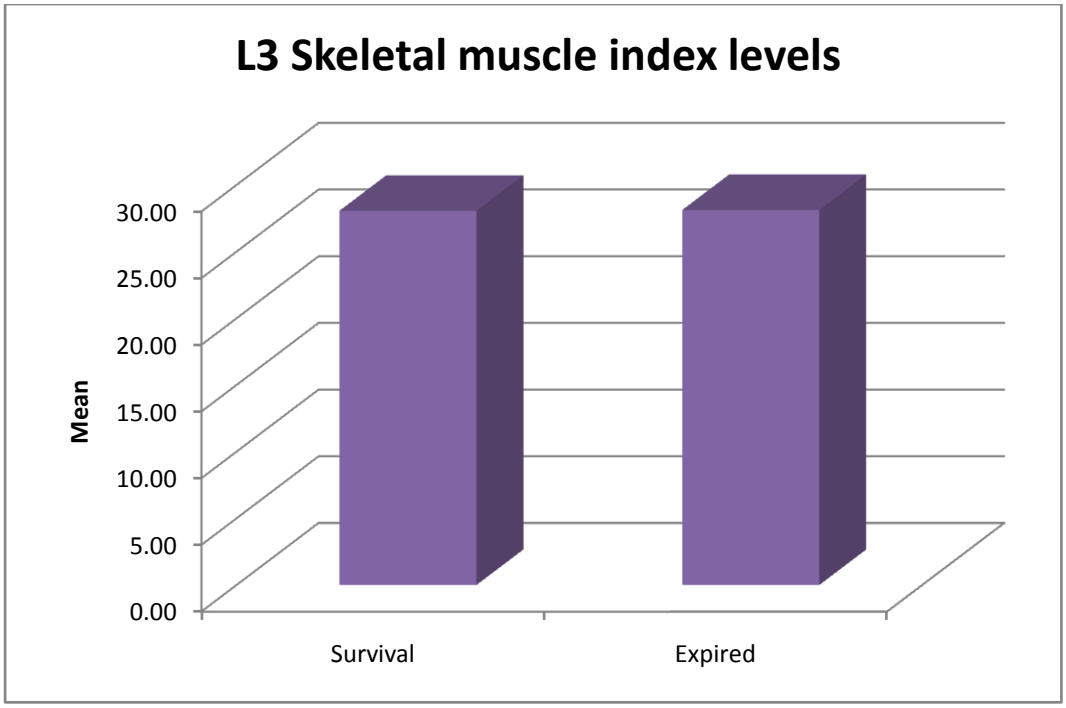


Figure 20B: Correlation of survival with L3SMI

CORRELATION OF SURVIVAL WITH CTP AND MELD SCORES

Table 20: Correlation of survival with CTP and MELD scores in patients of liver cirrhosis with sarcopenia

	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
CTP score	9.96	1.93	10.82	2.25	-2.344	0.021	-1.58	-0.13
MELD score	19.64	6.90	23.71	7.93	-3.123	0.002	-6.64	-1.49

Sarcopenic patients with lower CTP and MELD scores had higher survival.

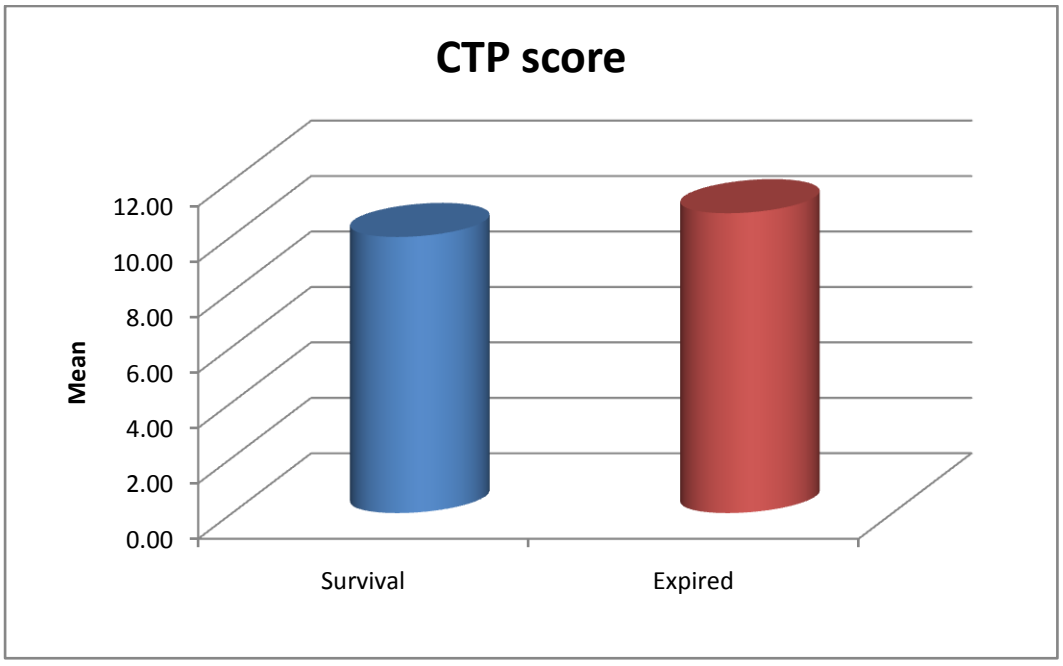


Figure 21A: Correlation of survival with CTP score

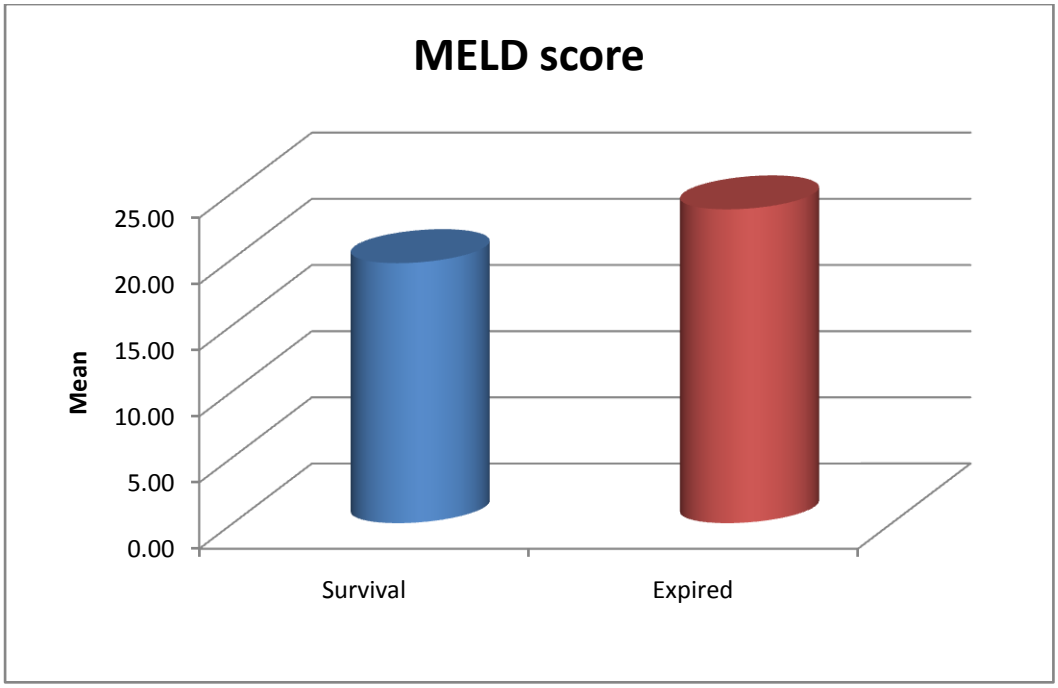


Figure 21B: Correlation of survival with MELD score

Table 21: Baseline characterstics of all patients

N=161	Survival		Expired		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
Height	164.12	8.45	173.25	37.97	-2.258	0.025	-17.12	-1.15
Weight	64.35	10.84	71.76	11.90	-4.083	0.000	-10.98	-3.82
BMI	24.04	4.76	24.55	5.96	-0.593	0.554	-2.17	1.17
HB baseline	9.68	2.36	9.80	2.91	-0.261	0.794	-1.03	0.79
TLC baseline	11.87	6.94	11.71	7.42	0.129	0.898	-2.34	2.66
NA+	131.52	7.29	132.74	6.11	-1.034	0.303	-3.55	1.11
Neutrophil baseline	75.78	12.99	75.96	10.38	-0.084	0.933	-4.40	4.04
INR	1.41	0.72	1.44	0.33	-0.326	0.745	-0.22	0.16
Bilirubin T baseline	6.90	7.65	8.01	8.88	-0.839	0.403	-3.74	1.51
Albumin baseline	2.71	0.62	2.66	0.50	0.606	0.545	-0.13	0.24
Creat	1.09	1.11	1.29	0.73	-1.225	0.223	-0.51	0.12
Gait velocity	0.66	0.20	0.53	0.15	-8.456	<0.0001	-1.09	-0.68
Hand Grip strength	20.43	7.96	15.14	6.95	4.359	0.000	2.89	7.69
Skeletal muscle index level	28.87	7.19	27.78	6.31	0.982	0.328	-1.10	3.27
CTP score	9.90	1.97	10.73	2.22	-2.492	0.014	-1.48	-0.17
MELD score	20.09	7.10	23.79	7.75	-3.143	0.002	-6.03	-1.38

This tables describes baseline characterstics of all patients irrespective of the presence or absence of sarcopenia. This table shows that patients who had less weight had significantly longer survival. Patients with higher gait velocity, and stronger hand grip strength had a longer survival, clearly dipicting that sarcopeni impacts survival in patients with cirrhosis. There was less survival in patients with advanced cirrhosis as seen with relation to CTP and MELD scores.

DISCUSSION

Cirrhosis is an irreversible pathology. It is classified as compensated and decompensated cirrhosis. Decompensation occurs in the form of ascites, encephalopathy and UGI bleed. Median survival of compensated cirrhosis is 12 years and that of decompensated cirrhosis is 2 years. This leaves as with therapeutic window of almost 10 years where therapeutic intervention can slow the progression of disease from compensated to decompensated disease. To prevent progression removal of etiological factors (e.g. alcohol, HBV, HCV, obesity) is the foremost step.

There have been studies on various methods (e.g. - statins) to slow down this progression or may be even revert it. There are various prognostic scores like the CTP score/MELD score for predicting survival and long term prognosis in cirrhosis. But these scores are predominantly based on laboratory parameters and do not take into account the functional capacity of cirrhotic patients.

Sarcopenia is the loss of muscle mass and strength. Sarcopenia is well established as a prognostic factor/factors to assess friability in geriatric populations and patients who require ICU care. This seems logical to investigate sarcopenia as a prognostic model for patients of cirrhosis and may be even devise therapies that reduce its progression. This study aimed to find the prevalence of sarcopenia in patients with advanced cirrhosis and its impact on complications and survival.

This was a single centre, investigator initiated, prospective, observational study. It was done on inpatient of department of gastroenterology Dayanand medical college and hospital Ludhiana. Patients were included in the study from Feb 2018 to November 2018 and there were followed up for survival in June 2018. Patients included in the study earlier had more than six months of follow up.

161 patients were included in the study after ruling out all the exclusion criteria and these patients underwent handgrip strength measurement, gait velocity measurement and CT section at L3 level at the time of enrolment. These patients were recorded for their baseline laboratory

parameters, presence of complications as described earlier. These were followed up for survival after 6 months of enrolment. 161 patients completed the follow up were included in analysis. One patient of Hepatocellular carcinoma was included. This patient had been treated for HCC and was on follow up surveillance. A total of 161 patients were included in the study. Of these 161 patients 121 were males and 40 were females. This difference in the presence of cirrhosis between the sexes was significant with a p value of <0.01. This highlights the increased prevalence of cirrhosis in males especially advanced cirrhosis.

Most common etiological factor of cirrhosis was alcohol in our study population. This was present in 101 out of 161 patients of study population. The role of alcohol as an etiological factor of cirrhosis vs other etiologies was the most significant with a p value of <0.01. The second most common etiology recorded was patients with NASH related cirrhosis with 37 patients out of 161 having NASH as an etiological factor for cirrhosis.

There was no significant difference in laboratory parameters such as Haemoglobin, Total Leucotye Count, PTI-INR, Bilirubin (Total), Albumin and creatinine at baseline in the males and females of the study population.

Coming to measures for assessment of sarcopenia there were significant difference in the gait velocity among males and females of the study population. Males having a higher mean gait velocity of 1.24 m/s vs 0.66 m/s of females. Mean hand grip strength in Males was higher at 18.10 dynes/cm^2 as compared to that of females at 15.37 dynes/cm^2.

The mean L3 SMI in males was higher at 29.38 as compared to females at 24.71. This difference was significant correlating with general consideration of males having higher muscle mass than females.

Comparing CTP and MELD scores in the study population. Mean CTP score in the study population differed significantly among males and females with mean CTP score in males being 10.97 while in females

being 9.58 with a p value of 0.18.This denotes that males were at an advanced stage of cirrhosis as compared to females on the contrary no significant difference was seen in the MELD score between the study population. This comparison highlights the facts that CTP score has ascites and hepatic encephalopathy as a parameter beside laboratory values while MELD score only has laboratory values.

As noted earlier there was no significant difference in the laboratory parameters of bilirubin, INR, albumin and creatinine in the study population so not much significant difference is expected in the study population.

There was significant difference in ascites presence in the study population with males having ascites and advanced cirrhosis as compared to females with a p value of 0.043.

On application of normative values of sarcopenia derived in normal Indian population by Dr. Sidhu[123] et al we found that 131 patients out of a total 161 patients were found to be sarcopenic. The prevalence of sarcopenia in cirrhotics was found to be 81%. This percentage of sarcopenia in cirrhosis is a bit higher than the range what is usually qoated in studies of 40-70%.

There was significant difference in the survival rate in males and females patients who had sarcopenic cirrhosis. 95% of cirrhotic male patients who had sarcopenia died as compared to 5% of sarcopenic females. The difference was significant with a p value of 0.00 implying that sarcopenia is a poorer prognostic factor for male patients with cirrhosis as compared to females with cirrhosis.

Presence or absence of ascites did not affect the survival of 131 patients of sarcopenic cirrhosis at 6 months follow up. This may be explained by the fact that the follow up period was 6 months may be longer follow up might better elicit the impact of ascites in the patient of cirrhosis with sarcopenia on survival.

Presence of other complications of cirrhosis i.e. hepatic encephalopathy and bleeding had worse effect on survival independent of the presence of sarcopenia. They were an independent factor in predicting mortality.

Presence of hepatic encephalopathy had a worse effect on survival. There was significant difference in survival at 6 months. 27% of patients with sarcopenia with hepatic encephalopathy died at 6 months as compared to 9% of patients.

Similarly other decompensating event UGI bleed had a worse effect on survival with 13% of sarcopenic patients with UGI bleed dying as compared to only 3% who did not had UGI bleed.

Our study did not find any significant correlation of Total leukocyte count with survival. So we could not find any correlation with sepsis. This could be because total leukocyte count is also a marker of inflammation in addition to infection. Further studies are needed in this correlation may be by blood cultures or procalcitonin levels.

On correlating etiology of cirrhosis with survival we found that alcohol being the most common etiology for cirrhosis was also the factor responsible for highest mortality among different etiologies for cirrhosis. 35% of patients with alcohol related cirrhosis died during follow up of 6 months. p value for this difference is significant at 0.00. This might be explained by the fact that a substantial number of these patients may be acute on chronic liver failure where alcohol might be the inciting factor for acute component of chronic liver failure as well. This has high short term mortality which is reflecting in our study.

Patients with less weight correlated with a longer survival. There was no significant difference in survival with respect to height and BMI.

There was no correlation of laboratory parameters namely haemoglobin, total leukocyte count, INR, total bilirubin, albumin and creatinine levels at baseline with survival of 6 months.

Gait velocity was higher in survivors as compared to non survivors this difference was significant. There was significant correlation of hand grip strength with survival at 6 month .the patient who survived had stronger hand grip at baseline than those who died with a p value of <0.01(significance). This finding correlates with the fact that presence of sarcopenia correlates with decreased survival in patients with liver cirrhosis.

There was no significant correlation of L3SMI levels with survival at 6 months. In the FrAILT Study[124], non survivors vis - a - vis those who were transplanted, still waiting, or removed from the wait-list for other reasons, exhibited poor muscle function as demonstrated by the lower grip strength (p=0.049) and lower Short Performance Physical Battery score (p=0.037). Survival did not correlate with SMI. Muscle mass quantification (i.e., skeletal muscle index on cross-sectional imaging), a static measure, fails to capture the loss of muscle strength or performance that potentially occurs as a result of intramuscular fat accumulation and other biological changes in muscle structure in patients with cirrhosis.[125,126]

In a prospective study of 159 outpatients patients with cirrhosis (MELD. 10+3 : 60% Child A), the authors found that the combination of body mass index (CT SMI) and thigh muscle thickness (measured by ultrasound) can identify male and female patients with sarcopenia using the area under the ROC curve values of 0.78 and 0.89, respectively.[127] In the reply to this manuscript, Topcu et al[128], commented that gait speed – a measure of muscle performance was not performed in the above study. Another possible confounder in this study vis – a vis sarcopenia is the fat infiltration in the muscles. Because muscle mass plus the fat content of the muscles is taken into account rather than lean muscle mass when ultrasound-guided measurement is performed, obesity may lead to underestimation of sarcopenia.

Survival at 6 months correlated with CTP and MELD scores. The higher the CTP scores more is the severity of cirrhosis. These CTP scores were significantly different in survivor and non survivor population with higher mean scores in non survivors as compared to survivors.

Similarly there was significant difference in survival in patients having higher MELD then those having a lower MELD with higher MELD correlating with poor survival.

There are many strengths of this study. First, this is first of a kind study to assess the prevalence of sarcopenia and its impact on the survival in

cirrhosis, done in Indian population. Second, this was a prospective study to include patients with advanced cirrhosis which contrasts most previous studies done on this subject which were retrospective and mainly included Child A cirrhosis patients. Third, this study included parameters to assess sarcopenia in all three spheres, namely muscle mass, muscle strength and muscle performance. Fourth, it had correlation with other prognostic markers of cirrhosis i.e. CTP and MELD score. Fifth this study also correlated the impact of sarcopenia and the presence of decompensated cirrhosis with survival at 6 months. This study forms a base for further research in this subject.

There were limitations too. First this was a single center study. Second the criteria to assess muscle mass that is L3 SMI index did not have significant correlation with survival. Further studies are needed in this regard to have a proper significance of this test in relation to sarcopenia. Third, there was a relatively smaller female population in our cohort which limited the ability to draw conclusions based on gender. Fourth, this study had a limited number of patients in non sarcopenic arm paving way for Type 2 error because of which true impact of sarcopenia on survival could not be adequately determined.

SUMMARY AND CONCLUSION

Prognostication of cirrhosis is a complex process with multiple factors affecting survival. Sarcopenia is a universal phenomenon with aging. Impact of sarcopenia as a prognostic marker in patients of liver cirrhosis has not been evaluated in a proper prospective trial till date. This study intends to do just that. This study has included all three components of assessment of sarcopenia i.e. muscle strength, muscle mass and muscle performance. Methods to assess these variables are not cumbersome to the patients as well as to the physicians. Significant correlation was observed between patients of sarcopenic cirrhosis and presence of complications of cirrhosis (ascites, bleed, hepatic encephalopathy). The prevalence of sarcopenia in patients with cirrhosis was found to be 81%, which denotes that a large number of advanced cirrhosis patients admitted in our wards are having sarcopenia.

This study opens more research questions in this field. This study helps to know the impact of sarcopenia in patients with compensated and decompensated liver cirrhosis. Research in this field may help devise strategies based on nutrient supplementation/BCAA supplementation to improve or reverse sarcopenia and have a favorable impact on the prognosis of patients with liver cirrhosis.

To conclude, there is a high prevalence (81%) of sarcopenia in patients with advanced cirrhosis. Sarcopenia impacts survival in presence of complications (ascites, bleeding, hepatic encephalopathy) in patients of cirrhosis.

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ID	Sex	Height	Weight	BMI	HB baseline	TLC Baseline	NA+	Neutrophil baseline	INR	Bilirubin T baseline	Albumin Baseline	CREAT	ASCITES (BASE)	Gait velocity	Hand Grip strength	Sekeltal muscle index level	Chair Stand EDIT	CTP score	MELD score	Follow up	Duration of Survival (Months)	Etiology	SARCO
1-001	M	164	61.8	22.98	9.4	8.5	138	63.3	1.87	13.47	2.8	0.71	YES	0.89	27.4	41.2	17.04	12	24	Survive	6	Alcohol	Y
1-002	M	177	58.5	18.67	10.1	2.38	139	66.8	1.24	1.43	3.1	0.52	NO	0.86	13.7	31.2	20.3	11	18	Survive	6	Alcohol	Y
1-003	M	175	55.5	18.12	5.8	19.2	148	84.4	1.2	0.72	2.8	1.23	NO	-	6.9	25.6	30.2	7	35	EXpire	1	Alcohol	Y
1-004	M	155	65.3	27.18	7.2	16.5	141	82.5	0.98	0.85	2.9	1.18	NO	0.45	10.8	38.9	25.3	5	23	EXpire	1	HCV	Y
1-005	M	170	58.6	20.28	13.2	18.7	131	76.7	2.25	32.2	3.5	3.2	YES	0.35	10.3	27.6	26.6	11	30	EXpire	2	HCV and HCC	Y
1-006	M	161	44.7	17.24	9.4	4.9	-	67.5	1.23	1.24	2.7	1.1	NO	0.88	12.3	35.8	25.3	8	10	EXpire	1	Alcohol	Y
1-007	M	173	86.2	28.80	11.8	9	137	81.9	1.48	2.6	2.7	0.73	NO	0.76	12.3	20.3	31.2	12	32	EXpire	1	Alcohol	Y
1-008	M	166	62.9	22.83	7.6	5.8	128	65.2	0.8	10.27	2.7	0.88	YES	0.2	15.6	38.9	25.3	13	30	EXpire	1	Alcohol	Y
1-009	M	175	82.2	26.84	15.1	5	127	63.8	0.4	12.7	3.7	0.07	YES	0.1	16.6	22.2	25.3	12	29	EXpire	3	Alcohol	Y
1-010	M	176	80.2	25.89	9.6	20.8	123	89.1	1.63	24.022	2.8	1.19	NO	-	12.8	31.1	25.3	8	26	EXpire	1	HCV	Y
1-011	M	172	72.3	24.44	7.5	13.3	135	84	1.77	13.11	3.6	1.1	YES	0.95	15.3	26.6	15.23	11	23	Survive	6	HCV	Y
1-012	M	173	60.8	20.31	13.7	11.4	122	77	1.28	5.84	2.9	0.51	YES	0.4	24.6	35.2	25.3	9	16	EXpire	2	Alcohol	Y
1-013	M	172	75.5	25.52	9.8	8.5	132	76	1.42	3.25	3.1	0.66	YES	0.69	12.6	16.9	35.6	11	15	EXpire	1	Alcohol	Y
1-014	M	173	76.1	25.43	8.7	5.5	133	57.7	1.33	2.83	2.8	1.54	YES	0.57	8	15.2	29.6	11	18	EXpire	1	Alcohol	Y
1-015	M	175	90.9	29.68	7.4	14	132	70	1.23	23.29	2.1	1.08	YES	0.83	28.1	36.3	25.3	14	27	Survive	6	Alcohol	Y
1-016	F	160	73.6	28.75	7.9	4.7	133	70.4	-	27.14	2.7	0.45	NO	0.58	10.3	28.6	30.3	10	30	EXpire	1	NASH	Y
1-017	M	145	72.2	34.34	14	19.3	143	89.5	1.38	7.46	4	1.04	NO	0.6	15.5	36.3	25.3	9	18	Survive	6	Alcohol	Y
1-018	M	175	73.5	24.00	9.3	14.8	133	72.6	1.77	26.6	2.7	0.72	YES	-	26	24.2	15.3	14	25	Survive	6	Alcohol	Y
1-019	M	167	94.5	33.88	10.8	12.9	127	64.7	1.72	33.9	2.4	0.74	NO	0.63	32.8	26.3	17.5	11	26	Survive	6	Alcohol	Y
1-020	M	168	82.2	29.12	8.1	14.7	129	79.7	1.83	4.35	2.6	1.52	YES	0.45	10.4	22.3	20.3	14	23	Survive	6	Alcohol	Y
1-021	M	167	63.2	22.66	12.5	7.9	139	80.5	0.9	23.1	3.8	1	NO	0.73	32.8	29.6	18.06	9	23	Survive	6	Alcohol	Y
1-022	M	168	69.3	24.55	10.4	6.1	134	94	1.5	1.14	2.7	0.88	YES	0.5	21.3	21.2	31.2	11	26	EXpire	1	Alcohol	Y
1-023	M	162	23.4	8.92	7.2	10.5	145	75.5	1.2	6.55	1.7	2.57	NO	0.3	23.4	34.5	25.3	13	34	Survive	6	Alcohol	Y
1-024	M	160	67.3	26.29	11.1	18.3	136	90	1.48	2.11	2.2	2.4	YES	0.2	31.3	32.3	15.3	12	22	Survive	6	Alcohol	Y
1-025	M	175.5	80.2	26.04	14.5	3.5	-	75	1.5	8.94	2.8	0.56	YES	0.47	20.6	31.2	25.3	11	19	Survive	6	NASH	Y
1-026	M	170	70.2	24.29	10.9	9.9	138	81	1.12	2.91	3.11	0.63	YES	0.2	27.8	23.3	20.9	11	12	Survive	6	Alcohol	Y
1-027	M	165	71.4	26.23	11.9	3.9	135	48.9	1.02	1.32	2.92	0.54	NO	0.83	16	31.5	25.3	8	10	Survive	6	Alcohol	Y
1-028	M	170	62.2	21.52	8.3	14.3	136	90.5	1.11	1.25	2.3	0.66	NO	0.3	9.2	29.6	36.6	8	8	EXpire	1	Alcohol	Y
1-029	M	165	52.3	19.21	12.4	5.1	133	86.4	1.23	6.87	3.5	1.7	NO	-	18.1	35.6	25.3	9	21	Survive	6	Alcohol	Y
1-030	M	475	84.5	3.75	7.8	6.5	131	82.8	1.66	3.3	2.13	1.83	YES	0.65	18.9	31.5	35.5	13	22	EXpire	1	Alcohol	Y
1-031	M	169	85.2	29.83	8.2	5.43	126	76.4	1.59	18.5	2.1	0.85	YES	-	15.5	23.3	16.3	12	29	Survive	6	Alcohol	Y
1-032	M	170	62.2	21.52	10.9	29.9	137	96.2	1.67	5.64	2.4	1.39	YES	0.58	18.1	28.5	32.2	12	22	EXpire	1	Alcohol	Y
1-033	M	177.5	85	26.98	12	4.7	-	69	1.07	2.53	2.31	0.51	NO	0.58	8.2	36.6	29.6	10	11	EXpire	1	Alcohol	Y
1-034	M	163	88.6	33.35	8.5	44.2	-	94.5	1.23	9.27	2	1.01	YES	-	11.2	35.5	36.3	15	25	EXpire	2	Alcohol	Y
1-035	M	162.5	67.3	25.49	11.3	11.7	123	85.4	1.48	6.38	2.45	1.2	YES	-	26.7	32.2	15.3	13	20	Survive	6	Alcohol	Y
1-036	M	162	80.3	30.60	10.2	6.1	129	-	1.16	17.17	2.6	0.44	YES	0.63	22.4	26.6	17.4	11	19	Survive	6	Alcohol	Y
1-037	M	162	74.6	28.43	12.6	9.4	130	88.7	1.28	2.67	2.5	0.85	NO	-	29.6	23.3	13.3	9	13	Survive	6	Alcohol	Y
1-038	M	163	63.3	23.82	10.4	6.1	125	59.7	1.3	2.88	3	0.77	NO	-	0	26.3	32.2	8	13	EXpire	1	Alcohol	Y
1-039	M	170	64.7	22.39	10.8	13.6	-	79.1	1.86	3.86	2.2	1.21	YES	0.88	20.3	32.3	34.2	14	20	EXpire	1	Alcohol	Y
1-040	M	166	95.5	34.66	9.4	20.8	125	83.6	1.17	2.85	2.1	0.84	YES	0.1	22.3	35.3	25.3	12	12	EXpire	3	Alcohol	Y
1-041	M	171	68.3	23.36	11.4	10.3	127	90.2	1.94	26.31	2.15	1.53	YES	0.1	32.9	34.91	14.2	13	30	Survive	6	Alcohol	Y
1-042	M	151	77.8	34.12	15.8	16.2	-	68	1.23	22.25	3.6	0.85	NO	0.3	0	24.4	25.3	10	27	EXpire	1	Alcohol	Y
1-043	M	171	71.3	24.38	7.9	21.7	130	81	1.04	1.36	2.9	0.8	NO	1.01	39.1	28.6	25.3	7	8	Survive	6	Alcohol	Y
1-044	F	150	68.6	30.49	7.8	17.76	-	89.8	1.1	2.72	2.9	1.27	YES	0.93	16.5	26.6	17.05	9	14	Survive	6	Alcohol	Y
1-045	M	173	84.8	28.33	12.3	19.6	118	85.9	1.2	4.11	2.35	1.93	YES	0.4	24.2	31.2	25.3	15	27	EXpire	4	HCV	Y
1-046	M	164	53.6	19.93	8.1	9.2	135	83	1.45	29.6	2.2	3.11	YES	0.68	23.3	22.3	32.3	13	34	EXpire	2	NASH	Y
1-047	M	165	56.6	20.79	8.6	7.3	126	81.7	1.38	8.58	2.8	0.51	YES	0.86	0	34.6	25.3	12	18	Survive	6	Alcohol	Y
1-048	M	170	53.3	18.44	9.9	11.6	133	73.4	1.03	20.4	2.57	1.38	YES	0.4	6.2	31.2	25.3	11	21	Survive	6	Alcohol	Y
1-049	M	168	52.2	18.49	8.6	15.1	-	80.5	1.81	1.84	2.4	0.73	YES	0.2	21.23	30.2	25.3	11	15	EXpire	1	Alcohol	Y
1-050	M	174	56.6	18.69	11.2	7.4	-	78.5	1.22	0.97	3.2	1.63	NO	0.66	25.3	28.2	25.3	8	13	EXpire	1	Alcohol	Y
1-051	M	168	53.3	18.88	11	14.6	131	75.2	1.5	1.02	2.35	1.12	YES	0.65	0	29.6	30.23	13	27	EXpire	1	Alcohol	Y
1-052	M	180	68.6	21.17	10.9	10.5	135	78.3	1.91	3.56	2.52	1.42	NO	0.67	20.3	25.5	32.3	11	30	EXpire	1	Alcohol	Y
1-053	M	171	53.6	18.33	8.9	3.8	138	74.5	1.56	2.56	2.83	1.26	YES	0.2	15.6	22.3	31.1	12	23	EXpire	3	Alcohol	Y
1-054	M	161	73.4	28.32	7.9	13.92	135	9.8	1.65	3.55	2	1.94	YES	0.74	28	25.6	13.3	12	23	Survive	6	Alcohol	Y
1-055	F	157	63.6	25.80	9.5	7.4	127	78.5	1.2	6.41	2.8	1.8	YES	0.63	17.6	19.6	36.3	13	27	EXpire	1	Alcohol	Y
1-056	M	171.5	68.5	23.29	12.1	11.7	139	76.3	1.39	1.83	3.4	0.87	NO	0.6	21.2	23.3	25.3	8	12	EXpire	1	NASH	Y

ID	Sex	Height	Weight	BMI	HB baseline	TLC Baseline	NA+	Neutrophil baseline	INR	Bilirubin T baseline	Albumin Baseline	CREAT	ASCITES (BASE)	Gait velocity	Hand Grip strength	Sekeltal muscle index level	Chair Stand EDIT	CTP score	MELD score	Follow up	Duration of Survival (Months)	Etiology	SARCO
1-057	M	175	87.5	28.57	5.8	7.7	139	67.5	1.73	2.47	2.87	1.12	NO	0.86	20.3	24.5	32.2	10	17	EXpire	1	Alcohol	Y
1-058	M	153	76.6	32.72	7.6	6	132	72.8	1.68	1.33	2.8	1.1	YES	0.69	20.6	21.2	36.6	10	14	EXpire	1	Alcohol	Y
1-059	M	160	65.6	25.63	14.6	9.3	-	65.7	1.27	1.25	2.5	1.09	NO	0.53	0	23.3	35.2	9	11	EXpire	1	Alcohol	Y
1-060	F	160	84.2	32.89	8	11.6	-	88.2	1.23	3.45	2.16	2.2	YES	-	11.1	23.3	34.5	15	36	EXpire	2	NASH	Y
1-061	M	176.6	63.3	20.30	13	11.6	141	69.1	1.8	3.55	3.5	1.02	NO	0.69	16.8	25.5	17.03	10	18	Survive	6	Alcohol	Y
1-062	M	176	63.3	20.44	6.8	4.8	136	55.4	1.93	4.86	2	1.24	NO	-	15.3	34.5	35.6	9	22	EXpire	1	Alcohol	Y
1-063	M	172	62.3	21.06	15.9	5.1	138	70.6	1.16	15.26	3.13	3.2	YES	0.73	13.6	23.3	32.3	13	30	EXpire	1	Alcohol	-
1-064	F	150	56.3	25.02	11.5	11.5	126	85.6	1.32	3.48	2.74	2.9	YES	0.87	13.1	26.5	16.05	12	24	Survive	6	NASH	-
1-065	M	156	68.5	28.15	8	11.6	-	88.2	1.25	3.45	2.16	2.2	YES	0.95	14.4	20.3	30.2	15	36	EXpire	1	Alcohol	Y
1-066	M	171	62.3	21.31	13.6	7.9	130	85.8	1.71	1.82	2.5	1.2	YES	0.6	15.6	23.3	25.3	8	15	EXpire	1	Alcohol	-
1-067	M	154	69.3	29.22	14.6	7.7	136	61.6	1.33	3.56	3.8	1.5	YES	0.47	17.7	31.2	23.3	7	14	EXpire	1	Alcohol and HCV	Y
1-068	M	172	-	0.00	5.2	19.6	-	59.5	1.74	1.49	2.09	1.2	YES	0.75	0	32.3	24.2	10	14	EXpire	1	Alcohol	Y
1-069	M	172	78.6	26.57	6.5	8.4	125	55.3	1.74	1.38	1.98	0.7	YES	0.85	16.6	35.5	26.6	13	24	EXpire	6	Alcohol	Y
1-070	M	173	90.2	30.14	11.5	11.5	126	85.6	1.32	0.4	2.74	0.6	YES	0.65	29	23.6	15.6	12	10	Survive	6	HCV	Y
1-071	M	174	91.5	30.22	15.9	5.1	138	70.6	1.16	15.26	3.13	3.2	YES	0.71	12.3	26.6	21.3	13	30	EXpire	2	Alcohol	Y
1-072	M	166	81.5	29.58	4.8	5.2	127	74.5	1.78	12.8	2.1	0.4	YES	0.93	10.2	21.2	20.3	12	29	EXpire	3	HCV	Y
1-073	M	174	73.5	24.28	9.3	6.9	132	82.4	1.25	10.51	2.8	1	YES	0.82	13.7	20.2	23.3	11	29	EXpire	1	Alcohol	Y
1-074	M	170	65.6	22.70	6.9	17.6	131	66.6	1.56	15.2	3.2	2.4	YES	0.8	20.8	21	29.6	13	32	EXpire	4	Alcohol	Y
1-075	M	172	85.2	28.80	9.4	11	132	77.7	1.42	28.19	2.9	1	YES	0.94	15.6	26.3	24.5	9	23	EXpire	3	Alcohol	-
1-076	M	164	65.3	24.28	9.4	17.6	131	66.6	1.56	15.2	3.2	2.4	NO	0.1	12.1	24.5	30.3	13	32	EXpire	5	Alcohol	Y
1-077	M	170	62.2	21.52	4.8	5.2	127	74.5	1.78	12.8	2.1	0.4	YES	0.68	15.6	26.6	25.3	12	29	EXpire	4	Alcohol	-
1-078	M	151	58.9	25.83	9.3	6.9	132	82.4	1.23	10.51	2.8	1	NO	0.79	11.1	32.3	25.3	11	29	Survive	6	NASH	-
1-079	M	170	61.2	21.18	9.6	20.8	148	89.1	1.63	2.08	2.8	0.4	NO	0.1	18.3	29.6	25.3	9	11	EXpire	3	Alcohol	-
1-080	M	175	63.4	20.70	11.5	11.5	126	85.6	1.04	2.03	2.74	0.8	YES	0	33.1	22.3	18.5	9	10	Survive	6	HCV	-
1-081	M	172	71.4	24.13	8	11.6	-	88.2	1.2	3.45	2.16	2.2	YES	0.99	0	21.3	25.3	15	36	EXpire	3	Alcohol	-
1-082	M	172	62.3	21.06	10.9	10.5	135	78.3	1.91	3.56	2.52	1.42	NO	0.3	12.3	26.6	25.3	11	30	EXpire	6	Alcohol	-
1-083	M	150	61.5	27.33	8.6	10.9	147	67.1	1.02	2.04	3.44	0.7	YES	0.81	11	23.3	14.5	10	10	Survive	6	Alcohol	Y
1-084	F	164	63.3	23.54	6.9	17.6	-	66.6	1.56	1.06	3.2	1.04	YES	0.97	18.8	31.2	25.3	10	25	EXpire	3	HCV	-
1-085	M	165	59.3	21.78	13.1	4.4	120	56.3	-	0.74	3.6	1.2	NO	0.56	10	36.3	18.6	11	19	Survive	6	NASH	-
1-086	M	161	53.3	20.56	12.4	11.6	123	76.3	1.23	19.84	2.5	1.5	YES	0.1	12	42.3		14	32	Survive	6	Alcohol	-
1-087	M	161	56.6	21.84	7.9	21.7	139	81	1.04	1.36	2.9	1	NO	0.83	16	31.2	-	7	35	Survive	6	Alcohol	-
1-088	M	165	54.5	20.02	10.4	6.1	131	59.7	1.3	2.88	3	2	NO	0.1	24.5	32.3	-	8	13	Survive	6	Alcohol	Y
1-089	M	168	51.2	18.14	9.6	20.8	148	89.1	1.63	2.08	2.8	0.4	NO	0.2	32.3	29.6	-	9	11	Survive	6	Alcohol	Y
1-090	m	165	62.3	22.88	8.7	5.5	147	57.7	1.33	2.83	2.8	0.5	YES	0.47	26.6	35.6	-	11	18	Survive	6	Alcohol	Y
1-091	M	168	59.3	21.01	7.9	21.7	114	81	1.04	1.36	2.9	2.4	NO	0.2	36.3	26.6	-	7	8	Survive	6	Alcohol	Y
1-092	M	163	62.3	23.45	11.5	11.5	128	85.6	1.2	3.04	2.74	1.3	YES	0.6	25.6	31.2	15.02	12	24	Survive	6	Alcohol	Y
1-093	M	169	65.5	22.93	10.4	6.1	122	59.7	1.3	2.88	3	1.9	NO	0.68	26.6	36.3	-	8	13	Survive	6	Alcohol	-
1-094	M	165	62.2	22.85	6.9	17.6	133	66.6	1.56	0.42	3.2	0.9	NO	0.63	28.6	26.3	14.02	7	16	Survive	6	Alcohol	-
1-095	M	174	64.5	21.30	6.9	17.6	126	66.6	1.56	1.06	3.2	1.04	YES	0.97	27.3	21.3	13.02	10	25	Survive	6	Alcohol	-
1-096	M	175	61.2	19.98	9.6	20.8	135	89.1	1.63	24.022	2.8	0.7	NO	0.77	23.3	24.5	15.06	9	26	Survive	6	Alcohol	-
1-097	M	171	53.7	18.36	10.8	15.1	130	68	1.23	11	2.3	1	YES	-	22.3	21.23	15.3	11	33	Survive	6	Alcohol	Y
1-098	M	165	58.5	21.49	6.2	5.9	132	65	0.4	2.03	1.9	0.4	YES	0.83	25.6	22.3	-	11	10	Survive	6	Alcohol	Y
1-099	F	171	63.3	21.65	9.7	4.6	131	72	1.2	2.6	1.7	2.1	YES	-	16.4	25.6	17.6	11	18	Survive	6	NASH	Y
1-100	F	172	75.6	25.55	8.9	3.6	140	82	1.3	2.89	1.9	0.6	NO	0.89	15.5	26.6	16.6	10	17	Survive	6	NASH	Y
1-101	F	125	76.3	48.83	10.9	6	135	54	1.11	3.2	2.6	0.9	NO	0.86	15.6	21.3	15.6	8	19	Survive	6	NASH	Y
1-102	F	162	69.6	26.52	14.7	10.8	140	81	1.23	4.1	3	1.5	NO	-	18.6	23.3	16.6	8	16	Survive	6	NASH	Y
1-103	F	171	72.6	24.83	7.9	19.3	136	85	1.51	8.3	1.5	0.62	YES	0.85	16.5	26.6	17.03	9	22	Survive	6	NASH	Y
1-104	F	157	67.6	27.43	11.2	10.3	135	70	1.27	6.4	4.3	0.23	YES	0.68	15.5	22.3	16.3	9	24	Survive	6	NASH	Y
1-105	F	157	71.2	28.89	9.2	10.4	123	66	0.97	1.4	2.4	0.4	YES	0.75	12.3	23.3	15.6	8	13	Survive	6	NASH	Y
1-106	F	163	75.6	28.45	7.1	8.3	135	83	1.41	1.8	3.1	0.9	NO	0.88	15.6	22.3	16.6	7	19	Survive	6	NASH	Y
1-107	F	162	71.3	27.17	12.7	3.43	142	92	1.65	28.2	2.8	1.08	NO	0.88	13.3	21.3	15.3	9	33	Survive	6	NASH	Y
1-108	F	163	75.6	28.45	6.1	20.8	126	92	7.6	12.5	2.7	0.7	YES	0.86	14.5	22.3	17.5	10	17	Survive	6	NASH	Y
1-109	F	143	63.3	30.96	12.8	13.2	131	79	1.6	13.3	2.2	0.7	YES	0.95	15.6	26.3	16.5	8	21	Survive	6	NASH	Y
1-110	F	165	56.6	20.79	9.5	13.6	125	78	1.33	1.5	1.8	0.1	YES	0.95	15.6	24.5	16.6	8	13	Survive	6	NASH	Y
1-111	F	156	63.3	26.01	6.2	12.6	126	71	1.05	2.03	1.7	0.4	YES	0.48	12.3	24.2	16.6	11	16	Survive	6	NASH	Y
1-112	F	163	56.3	21.19	13.9	10.7	132	78	1.62	10.2	3	1	YES	0.2	13.3	25.6	14.5	8	24	Survive	6	NASH	Y

ID	Sex	Height	Weight	BMI	HB baseline	TLC Baseline	NA+	Neutrophil baseline	INR	Bilirubin T baseline	Albumin Baseline	CREAT	ASCITES (BASE)	Gait velocity	Hand Grip strength	Sekeltal muscle index level	Chair Stand EDIT	CTP score	MELD score	Follow up	Duration of Survival (Months)	Etiology	SARCO
1-113	F	165	65.6	24.10	6.6	12.3	126	72	1.25	5.3	2.3	0.4	YES	0.6	16.6	25.6	14.5	10	24	Survive	6	NASH	Y
1-114	F	168	56.6	20.05	10.1	11.1	121	82	1.05	2.04	2.7	0.9	YES	-	17.5	22.3	16.3	8	10	Survive	6	HCV	Y
1-115	F	167	51.2	18.36	11.5	5.5	141	53	1.14	1	3.4	0.4	YES	0.61	16.3	21.3	15.6	7	12	Survive	6	HCV	Y
1-116	F	163	52.3	19.68	10.1	10.5	129	78	1.04	4.05	2.3	0.9	YES	-	15.6	23.3	16.6	10	19	Survive	6	NASH	Y
1-117	F	165	63.3	23.25	11.9	15.5	129	77	0.4	6.3	3	1.02	YES	0.89	16.6	22.3	15.6	11	21	Survive	6	NASH	Y
1-118	F	165	53.3	19.58	8.1	11.3	125	88	1.32	2.2	1.8	1.03	YES	0.5	15.6	25.5	16.6	11	27	Survive	6	HCV	Y
1-119	F	152	53.3	23.07	7.9	21.1	123	93	1.2	1	2.6	0.9	YES	0.84	14	-	16.6	8	22	Survive	6	Autouimmune	-
1-120	F	163	52.3	19.68	6.9	19.1	124	88	1.2	7.1	2.8	0.4	YES	0.72	15.4	26.6	14.5	12	25	Survive	6	NASH	Y
1-121	F	165	63.3	23.25	10.9	18.2	132	90	1.91	0.8	3.6	1.03	YES	0.65	16.5	21.23	15.6	9	14	Survive	6	NASH	Y
1-122	F	163	51.6	19.42	7.4	6.3	125	65	1.9	5.3	3	0.9	YES	0.65	17.6	22.3	16.6	11	29	Survive	6	NASH	Y
1-123	F	157	63.3	25.68	5.9	12.8	132	81	1.75	0.7	2.6	0.7	YES	0.63	16.6	23.3	16.6	9	13	Survive	6	NASH	Y
1-124	F	156	65.6	26.96	8	7.2	141	69	1.61	2.3	2.4	0.5	YES	0.63	17.6	24.5	16.6	9	13	Survive	6	NASH	Y
1-125	F	167	68.6	24.60	6.3	15.8	132	81	1.36	3.2	2.2	10.2	YES	0.53	15.6	22.3	16.6	10	24	Survive	6	NASH	Y
1-126	F	165	53.3	19.58	8.9	7.9	120	69	1.02	11.7	2.8	2.03	YES	0.48	13.3	25.6	15.4	11	27	Survive	6	NASH	Y
1-127	F	145	52.3	24.88	9.5	7.3	121	67	1.63	3.4	2.3	1.09	YES	0.45	14.6	29.6	16.6	9	17	Survive	6	NASH	Y
1-128	F	154	53.3	22.47	8.3	4.8	130	72	1.26	4.1	2.3	1.03	YES	0.56	13.6	22.6	16.6	10	24	Survive	6	NASH	Y
1-129	F	165	56.6	20.79	6	7.9	135	68	1.51	1.2	2.1	0.5	YES	0.65	15.6	21.2	15.6	7	22	Survive	6	NASH	Y
1-130	F	171	53.3	18.23	7.2	10.2	123	84	1.23	11.3	2.1	0.9	YES	0.56	16.6	24.5	16.6	10	28	Survive	6	NASH	Y
1-131	F	165	52.3	19.21	9.1	12	121	80	0.9	25	3.1	1.05	YES	0.63	15.6	52.3	13.5	10	27	Survive	6	HCV	-
1-132	M	159	56.1	22.19	16.1	52.8	134	97.4	1.2	4	3.1	3.19	YES	0.56	16	52.1	15.6	8	30	Survive	6	HCV	Y
1-133	M	171	86	29.41	-	-	131	-	2.01	15.25	-	0.73	YES	0.45	27.5	35.6	16.5	13	25	SURVIVE	-	HCV	-
1-134	M	175	78	25.47	-	-	129	-	2.12	21.17	2.8	2.65	YES	0.63	20.3	39.6	29.6	11	37	EXpire	2	Alcohol	Y
1-135	M	180	72	22.22	6	7.9	135	68	1.51	1.2	2.1	0.5	YES	0.53	15.6	21.2	15.6	7	22	Survive	6	NASH	Y
1-136	M	165	61.2	22.48	-	-	129	-	1.5	1.89	2.8	0.45	YES	0.52	18	45.6	15.6	10	22	survive	6	Alcohol	Y
1-137	M	161	50	19.29	-	-	128	-	1.2	2.3	3.1	0.77	YES	0.23	28.1	29.6	16.6	8	19	SURVIVE	6	NASH	Y
1-138	M	161.5	53.6	20.55	-	-	138	-	1.26	1.97	2.1	0.8	YES	0.5	8.5	21.2	17.3	9	11	SURVIVE	6	HCV	-
1-139	M	171	68.5	23.43	-	-	128	-	1.67	5.67	2.3	0.65	NO	0.6	33.2	21.3	15.6	9	25	EXpire	6	Alcohol	-
1-140	M	171	64.6	22.09	-	-	128	-	-	-	-	-	YES	0.63	17.5	26.3	36.6	10	30	EXpire	6	Alcohol	Y
1-141	M	169	83.6	29.27	-	-	130	-	1.02	32.41	2.7	1.71	NO	0.35	-	-	-	10	33	EXpire	6	Alcohol	Y
1-142	M	165	61.2	22.48	-	-	113	-	1.02	8.13	3.2	0.71	YES	0.56	22.5	35.2	16.5	12	40	Survive	6	NASH	Y
1-143	M	156	70	28.76	-	-	136	-	1.17	1.11	4.2	0.7	YES	0.58	21.2	35.2	16.6	12	9	SURVIVE	6	NASH	Y
1-144	M	171	78	26.67	-	-	135	-	1.71	4.41	1.68	0.81	YES	0.56	26.2	45.5	13.2	12	18	EXpire	3	Alcohol	Y
1-145	M	171	78.4	26.81	-	-	136	-	1.51	4.73	2.2	0.84	YES	0.58	21	36.3	13.3	12	18	SURVIVE	6	Alcohol	Y
1-146	M	180	78.4	24.20	-	-	133	-	1.2	0.56	3.3	0.69	NO	0.57	29.2	48.6	13.6	8	9	SURVIVE	6	Alcohol	Y
1-147	M	172	75.5	25.52	-	-	133	-	1.41	-	-	-	YES	0.46	17.6	25.6	30.3	11	30	EXpire	6	Alcohol	Y
1-148	M	168	92.2	32.67	-	-	136	-	1.3	-	-	-	YES	0.53	15.6	35.6	26.6	9	30	EXpire	6	Alcohol	Y
1-149	M	168	92.2	32.67	-	-	141	-	0.9	2.51	2.6	0.96	YES	0.59	20.3	32.2	12.3	9	22	EXpire	6	Alcohol	Y
1-150	M	170	69.6	24.08	-	-	137	-	1.96	1.95	0.9	0.8	NO	0.45	45.4	36.6	13.3	5	19	SURVIVE	6	HCV	Y
1-151	M	169	71.7	25.10	-	-	138	-	1.02	17.53	3	0.63	YES	0.53	14.5	25.6	27.5	9	30	EXpire	6	Alcohol	Y
1-152	M	182	84.5	25.51	-	-	133	-	1.25	2.18	3.5	0.98	YES	0.46	18.9	35.6	29.63	9	16	EXpire	2	Alcohol	-
1-153	M	171	80.6	27.56	-	-	134	-	1.67	5.67	2.3	1.18	YES	0.65	24.1	36.6	30.3	9	22	EXpire	6	Alcohol	Y
1-154	M	167	67.8	24.31	-	-	138	-	0.9	3.12	2.9	0.76	YES	0.89	28.4	26.6	15.6	9	22	SURVIVE	6	Alcohol	-
1-155	M	172	93.6	31.64	-	-	145	-	1.43	23.97	3.2	1.14	YES	0.93	18.1	22.3	-	11	24	EXpire	3	Alcohol	Y
1-156	M	157	61	24.75	-	-	140	-	1.41	0.82	4.7	0.76	NO	0.68	31.3	46.3	13.3	6	9	SURVIVE	6	Alcohol	-
1-157	M	165	67.5	24.79	-	-	142	-	1.82	2.83	2.9	1	NO	0.68	33	32.3	13.6	8	9	SURVIVE	6	NASH	Y
1-158	M	161	58.8	22.68	-	-	138	-	1.26	14.7	2.2	1.16	YES	0.96	25.2	35.3	12.3	12	31	SURVIVE	6	HBV	-
1-159	M	162	81.8	31.17	-	-	124	-	1.83	4.37	2.49	0.71	YES	-	8.3	22.3	31.2	11	27	EXpire	2	Alcohol	-
1-160	M	165	67.3	24.72	-	-	118	-	1.18	-	-	-	YES	0.95	30.8	35.6	15.6	9	19	SURVIVE	6	Alcohol	-
1-161	M	169	60.4	21.15	-	-	131	-	1.44	1.92	1.3	1.92	YES	0.62	18.2	-	-	8	23	EXpire	2	Alcohol	-

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The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 31.08.2018 has approved the plan of thesis of Tarun Varshney, a student of your college for DM Medical Gastroenterology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Sarcopenia decreases the survival of patients with liver cirrhosis

Supervisor
Dr. Sandeep Singh Sidhu
Prof.,
Dept. of Gastroenterology,
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Co-Supervisor
Dr. Kavita Saggar
Prof. & Head,
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The student has to submit the four copies of thesis, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

SPSingh
Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

In

GASTROENTEROLOGY

OF

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

February, 2018

DR. TARUN VARSHNEY

DEPARTMENT OF GASTROENTEROLOGY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Sarcopenia decreases the survival of patients with liver cirrhosis
For the degree of	D.M. (Gastroenterology)
Name of the candidate	Dr. Tarun Varshney
Supervisor	Dr. Sandeep Singh Sidhu, Professor, Department of Gastroenterology, DMCH
Co-supervisor	Dr. Kavita Saggar, Professor & Head, Department of Radiodiagnosis, DMCH
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: A variety of nutritional disorders, such as protein-calorie malnutrition (PCM) and/or sarcopenia, which are frequently observed in patients with liver cirrhosis.

Aim of Study: 1.To assess the survival rate of patients of liver cirrhosis with sarcopenia.

2. To assess complications in patients of liver cirrhosis with sarcopenia.

3 . To assess prevalence of sarcopenia in patients of liver cirrhosis.

Materials & methods:

The study will be conducted on patients of Liver Cirrhosis attending the OPD and admitted in the Inpatient Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana

Clinical Significance: Studies on nutritional assessment in cirrhosis usually focus on one or few aspects of nutritional status and not on a full nutritional assessment combining information from medical, biochemical, nutritional, and body composition variables. Hence, the present study aims at a thorough assessment of nutritional status of cirrhotic patients using standardized methods to estimate the prevalence of sarcopenia.

Keywords: Sarcopenia, liver cirrhosis.

(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS"** exist in the Department of Gastroenterology, Dayanand Medical College & Hospital and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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Date : _____

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
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Department	Gastroenterology
Topic of Thesis	SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS
Likely date of appearing in PG examination	May 2020
Date of enrollment	11 September 2017
Name of Head of Department	Dr. Ajit Sood
1) Supervisor	Dr. Sandeep S Sidhu
2) Co-Supervisor(s)	Dr. Kavita Saggar

Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
	7. HOD Obst. & Gynae
	8. Legal Expert
	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved: Yes / No

Chairperson
Research Committee

Approved : Yes / ~~No~~

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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3	COURSE OF STUDY AND SUBJECT	DM Gastroenterology
4	DATE OF ADMISSION OF COURSE	11 September 2017
5	TITLE OF THE TOPIC	Sarcopenia decreases the survival of patients with liver cirrhosis

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

A variety of nutritional disorders, such as protein-calorie malnutrition (PCM) and/or sarcopenia, which are frequently observed in patients with liver cirrhosis.[1] PCM is associated with high morbidity and mortality due to an increased risk of complications in these patients.[2,3] Therefore, diagnosis of and intervention for PCM are essential to improve the outcome of patients with cirrhosis. Nutritional support, including branched-chain amino acid (BCAA) supplementation and frequent meals, is recommended by current guidelines.[4] Sarcopenia is characterized by the depletion of skeletal muscle mass, and is a predictor of morbidity and mortality in patients with Liver Cirrhosis.[5,6] Skeletal muscle mass is generally maintained by a balance between protein synthesis and protein breakdown. Cirrhotic patients have insufficient glycogen stores due to liver atrophy, and their energy generation pattern after an overnight fast is equivalent to that observed in healthy individuals after 2 to 3 days of starvation.[7] Such a catabolic state increases the consumption of amino acids as an energy source and accelerates the breakdown of skeletal muscle to release amino acids, resulting in sarcopenia.[8] Hence, a nutritional intervention can be an effective modality for improving sarcopenia associated with Cirrhosis.[9,10]

Predicting prognosis is crucial in the management of patients with cirrhosis. A number of prognostic models have been derived and validated. Since 2002, the MELD score has replaced the CTP score for organ allocation in patients waiting for Liver Transplantation in the United States, due to the advantage of including only objective laboratory variables and its superior ability to predict

short-term outcomes compared to the CTP score. However, the MELD score also has some drawbacks, including variability in laboratory parameters, misclassification of some patients with a low MELD score, and the lack of a nutritional status assessment.[11]

Many researchers have tried to improve the prognostic performance of the MELD score. Hyponatremia accurately predicts short-term mortality independently of the MELD score and is often associated with ascites, hepatorenal syndrome, and liver-related mortality.[12] Incorporating serum sodium into the MELD score, known as MELD-Na, improves its predictive ability, particularly for patients with a low MELD score.[13]

PREVALENCE OF SARCOPENIA IN CIRRHOSIS

Cross-sectional imaging studies have reported that the prevalence of sarcopenia is 30%-70% among patients with cirrhosis. This wide range is partly explained by the lack of an operational definition for sarcopenia in patients with cirrhosis, patient baseline characteristics, and diversity in the cause and severity of liver disease among studies Sarcopenia is more frequent in men than in women and in patients with a low BMI. The proportion of patients with sarcopenia is higher in those with alcoholic liver disease (80%) compared to other diseases (31%-71%). In some reports, CTP or MELD scores were predictors of sarcopenia, whereas others found that sarcopenia was not correlated with the degree of liver dysfunction assessed by conventional scoring systems (CTP or MELD score).[14]

Sarcopenia is an important prognostic factor in cirrhosis. Nutritional assessment is therefore crucial for identifying patients at risk or with already established malnutrition and refer them for nutritional intervention and

support. In the current literature, nutritional assessment of cirrhotic patients is performed using several tools and methods. However their accuracy is widely affected by the underlying disease and its complications. Studies on nutritional assessment in cirrhosis usually focus on one or few aspects of nutritional status and not on a full nutritional assessment combining information from medical, biochemical, nutritional, and body composition variables. Hence, the present study aims at a thorough assessment of the nutritional status of cirrhotic patients using standardized methods to estimate the prevalence of sarcopenia.

6.2 REVIEW OF LITERATURE

Mechanisms of sarcopenia in cirrhosis

Even though a large number of descriptive studies show the high clinical significance of sarcopenia in cirrhosis, mechanistic studies to identify how sarcopenia develops and the mediators of the liver muscle axis are much less well understood. Early studies have suggested that patients with cirrhosis have a number of reasons for malnutrition, primarily muscle loss, but the most important reasons are poor oral intake and lack of activity. However, 2 meta-analyses have suggested that supplemental nutrition does not improve clinical outcomes.[15] This is because patients with liver disease are believed to be in a state of anabolic resistance that prevents appropriate skeletal muscle responses to nutrient administration. Skeletal muscle mass is maintained by a balance between protein synthesis, breakdown and possibly the regenerative potential mediated by the myogenically committed stem cells, satellite cells. Studies in the portacaval anastomosis rat provided an explanation for human findings. Early after the anastomosis, there was increased skeletal muscle proteolysis with unaltered protein synthesis and later in the course, both protein synthesis and proteasome mediated proteolysis were lower. Interestingly, autophagy was increased in the muscle of cirrhotics even when ubiquitin mediated proteolysis was unaltered or decreased. A recent study reported lower protein synthesis markers in the skeletal muscle of patients with cirrhosis with decreased ubiquitin mediated but increased autophagy mediated proteolysis.[16] These data show that reduced protein synthesis and increased autophagy mediated protein breakdown contribute to ongoing skeletal muscle loss in cirrhosis.

Increased circulating and skeletal muscle expression of myostatin, a TGFβ superfamily member, have been reported in patients with cirrhosis. Myostatin inhibits protein synthesis and increases autophagy. Extensive studies have been performed on myostatin binding to its receptor on the skeletal muscle membrane and the regulation of protein synthesis by inhibition of mTORC1. In contrast, upstream regulation of myostatin is not as well studied, but hyperammonemia has been recognized as an activator of myostatin via an NFKB mediated mechanism.[17] Hyperammonemia is an activator of reactive oxygen species and this may be another mechanism of activating autophagy. Interestingly, ammonia disposal by the skeletal muscle is mediated via glutamate synthesis in the mitochondria followed by its conversion to glutamine in the cytosol that is transported to the circulation in exchange for leucine that is transported into the muscle. However, within the cell, leucine can either be used for peptide chain elongation or protein synthesis and for activation of mTORC1 by lysosomal transport. An alternate method of leucine metabolism in cirrhosis and potentially hyperammonemia is via mitochondrial oxidation to generate acetyl CoA as a source of energy.

Since the primary mechanism of skeletal muscle ammonia disposal is via cataplerosis (loss of TCA cycle intermediates by enzymatic reactions) of α ketoglutarate (αKG), one option is to increase anaplerosis (addition of 4 and 5 carbon TCA cycle intermediates). This can be achieved by either isoleucine or valine, both of which provide direct anaplerotic input or recent reports that suggest that leucine carbon is used to form αKG. The deamination/ transamination of amino acids as anaplerotic agents results in release of ammonia in a 1:1 stoichiometric ratio with only one net ammonia removed

during the formation of glutamine.[18] A novel approach is to provide cell permeable TCA cycle intermediate, αKG that provides the substrate to remove 2 molecules of ammonia in the muscle. A schematic overview of the current concepts in the pathogenesis of sarcopenia and contractile dysfunction in cirrhosis is shown in Figures 1 and 2.[19]

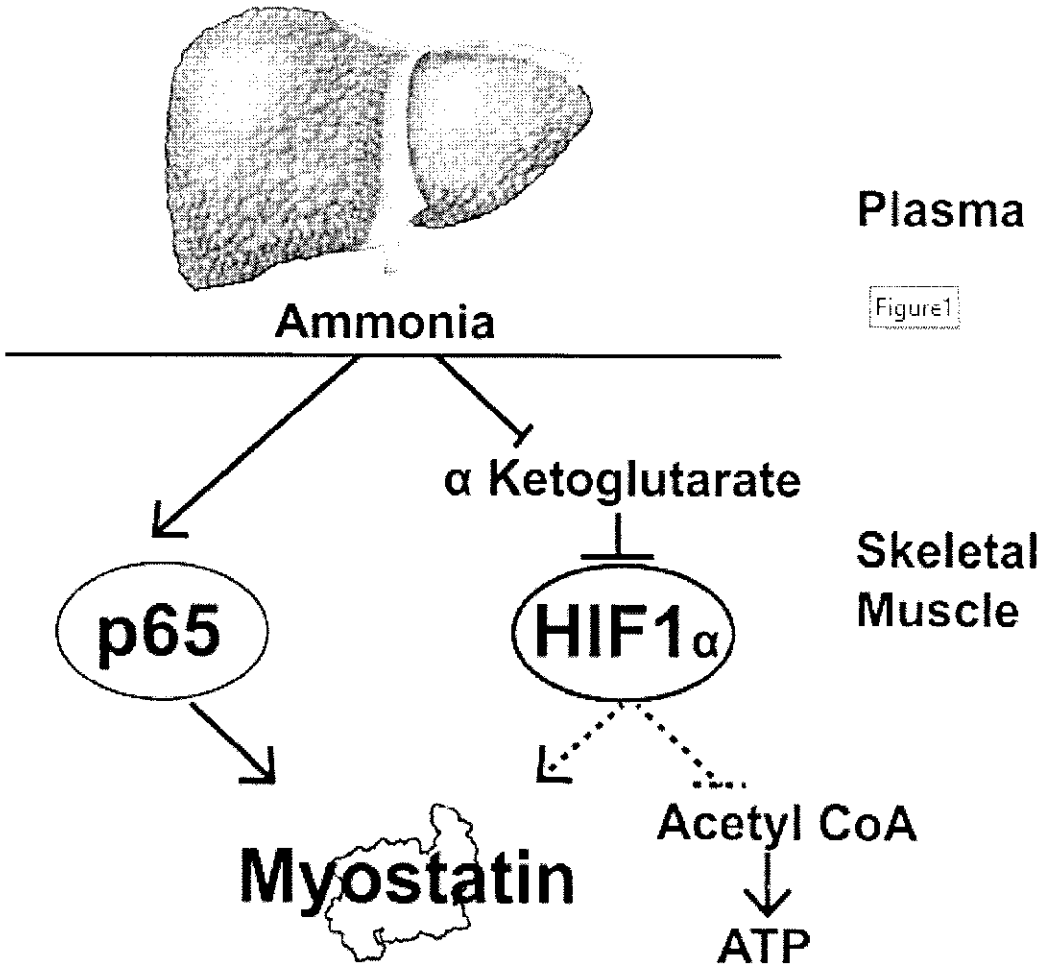


Figure 1. Overview of ammonia induced metabolic and signaling perturbations Impaired hepatic ureagenesis results in skeletal muscle hyperammonemia. Ammonia transcriptionally upregulates myostatin via a p65NFkB mediated mechanism and decreases α ketoglutarate by cataplerosis. Reduction in α ketoglurate can stabilize hypoxia inducible factor 1α (HIF1α) that in turn can activate myostatin and inhibit pyruvate to acetyl CoA oxidation (dotted lines are preliminary studies from our laboratory).

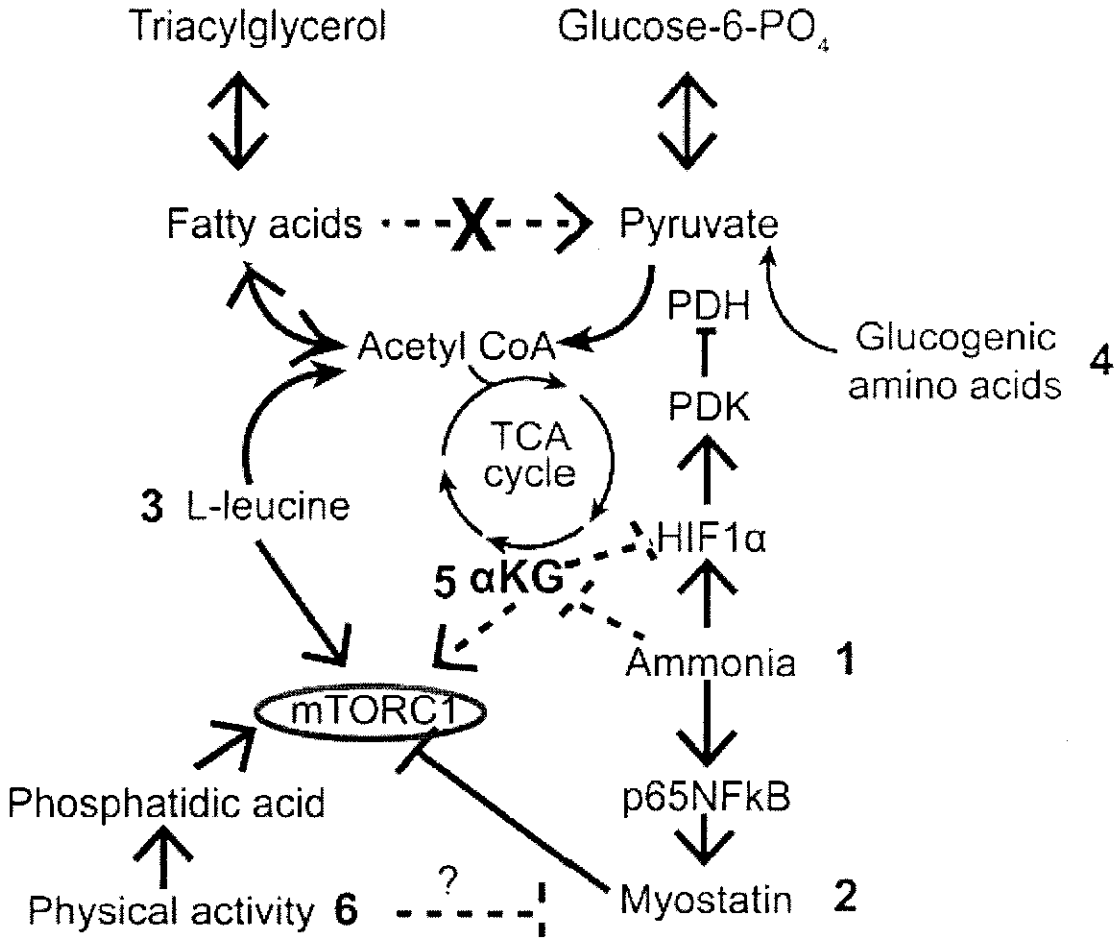


Figure 2. Metabolic abnormalities that contribute to and potential therapeutic targets

Accelerated lipolysis generates acetyl CoA from fatty acids due to impaired pyruvate dehydrogenase (PDH) by hypoxia inducible factor 1α (HIF1α) via pyruvate dehydrogenase kinase (PDK) and possibly directly by ammonia. Cataplerosis of α-ketoglutarate (αKG) by to form glutamate is a metabolic disposal pathway activated in the muscle during hyperammonemia. Lower αKG results in stabilization of HIF1α, decreased mTORC1 activation and decreased tricarboxylic acid (TCA) cycle flux and lower ATP synthesis. These perturbations contribute to lower protein synthesis. Homeostatic responses include the utilization of branched chain amino acids to provide anaplerosis for generate αKG (isoleucine, valine) and acetyl CoA (leucine, isoleucine) with

increased transport of branched chain amino acids from circulation for metabolic disposal. Ammonia via a p65NFkB mediated mechanism also activates myostatin that in turn inhibits mTORC1. These metabolic and molecular perturbations contribute to decreased sensitivity to anabolic stimuli (anabolic resistance) that can be potentially reversed by intervention at targeted sites.

Assessment of sarcopenia

Sarcopenia has garnered increasing interest among clinicians over recent decades and is now classed as a geriatric syndrome; the current definition is age-associated loss of skeletal muscle mass as well as diminished muscle strength and/or physical performance, which is associated with reduced physical capability, impaired cardiopulmonary performance, disability, and mortality among older people.[20] Skeletal muscle area derived from a single slice CT has become more easily reproducible, and reduces the radiation exposure required to only 2.6 millisieverts. Measuring cross-sectional muscle area at either the level of the third (L3) or fourth (L4) lumbar vertebrae has been shown to correlate well with total body muscle mass (r = 0.71), and it is now accepted as a safe and accurate means of estimating muscle mass. When adjusted for patient height to take stature into account it is referred to as skeletal muscle index (SMI will be calculated of Slice-O-matic software, version 4.3 (Tomovision), Montreal, QC, Canada).).L3 skeletal muscle index has been shown to be of higher accuracy in the diagnosis of sarcopenia in cirrhosis than anthropometry or DEXA scanning and is now the most commonly **employed** method in studies investigating sarcopenia in cirrhosis. Diagnostic criteria have been extrapolated from Cirrhosis populations.[21]

Multiple studies in cirrhosis which have employed this definition have produced clinically meaningful results and it is increasingly accepted as the most appropriate definition of sarcopenia when using cross-sectional imaging. Muscle strength was assessed by grip strength and measured using a dynamometer. The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand to make sure that the middle phalanx rested on the inner handle. The participant was allowed to perform one test trial. After this, three trials followed and the best score was used for analysis. Handgrip strength was expressed in kilogrammes (Kg).[22] Three trials for each hand were carried out and we used the highest value for diagnosing sarcopenia. Low handgrip strength was defined as <26 kg in men and <18 kg in women.[23] Usual gait speed (m/s) on a 4 meter course was used as an objective measure of physical performance and a slow walking speed was defined as a walking speed less than 0.8 m/s.

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To assess the survival rate of patients of liver cirrhosis with sarcopenia.
2. To assess complications in patients of liver cirrhosis with sarcopenia.
3. To assess period prevalence of sarcopenia in patients of liver cirrhosis.

7. MATERIALS AND METHODS

7.1 Source of Data

The study will be conducted on patients of Liver Cirrhosis attending the OPD and admitted in the Inpatient Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana. The subjects will be enrolled in a duration of March 2018 to September 2018 with cirrhosis and a follow up of one year.

7.2 METHOD OF COLLECTION OF DATA

The Investigator will also complete a full medical record regarding the cirrhosis, its aetology, complications, co morbidities. The severity of cirrhosis will be assessed using the Child-Pugh score and the MELD score, Furthermore, patients will participate in the following procedures:

- **Muscle mass:** L3 skeletal muscle index calculation (Slice-O-matic software, version 4.3 (Tomovision), Montreal, QC, Canada)
- **Muscle strength :Handgrip strength measurement**

Muscle strength was assessed by grip strength and measured using a dynamometer. The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand to make sure that the middle phalanx rested on the inner handle. The participant was allowed to perform one test trial. After this, three trials followed and the best score was used for analysis. Handgrip strength was expressed in kilogram's

(Kg).[22] Low handgrip strength was defined as <26 kg in men and <18 kg in women.[23]

- **Muscle performance status:** gait velocity measurement

Gait Speed Test (4-metre): Instructions:

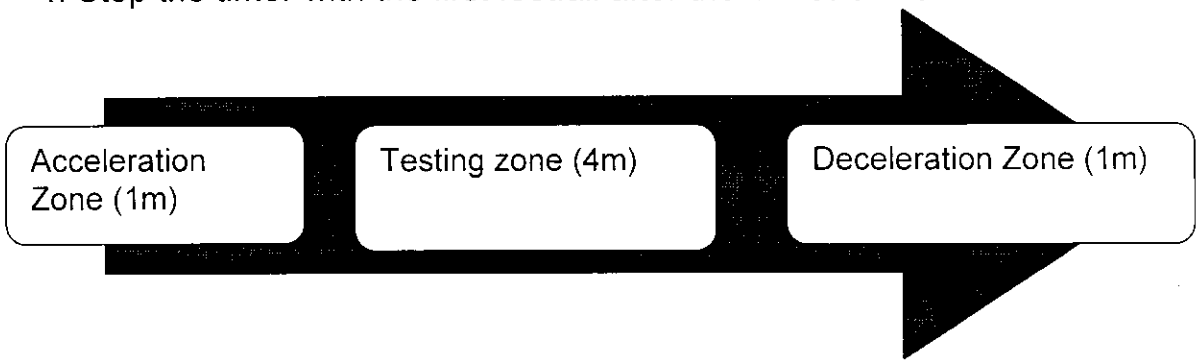
The test can be performed with any patient able to walk 4 meters using the instructions below:

1. Instruct the patient to walk at their normal pace. Patients may use an assistive device, if needed.

2. Ask the patient to walk down a hallway through a 1-metre zone for acceleration, a central 4-metre "testing" zone, and a 1-metre zone for deceleration (the patient should not start to slow down before the 4-metre mark).

3. Start the timer with the first footfall after the 0-metre line.

4. Stop the timer with the first footfall after the 4-metre line.



One year after the baseline assessment of the study samples, data will be collected regarding survival and development of complications of cirrhosis.

Normative Data of L3 SMI, Handgrip strength and Gait speed shall be calculated in Healthy individuals.

Sarcopenia indices shall be compared with CTP and MELD score to assess the best Predictor of survival of patients with cirrhosis.[24]

Clinical and laboratory Assessment

Baseline Clinical and blood biochemical data, will be obtained. Liver Function test, Renal function test, PTI/INR will be recorded.

Inclusion Criteria:

Adults with cirrhosis.

Exclusion Criteria:

Patients with hepatocellular carcinoma, in hepatic coma, with acquired immunodeficiency syndrome, with renal or pancreatic insufficiency, receiving enteral nutrition or being pregnant, will be excluded.

DURATION OF STUDY- The subjects will be enrolled in a duration of March 2018 to September 2018 with cirrhosis and a follow up of one year

OUTCOME

Primary Outcome: Survival at 1 year

Secondary Outcome

- Variceal bleed
- Ascites: Denovo or diuretic responsive or Refractory
- Overt Hepatic Encephalopathy
- Sepsis : Shock, pneumonia, SBP, UTI, Skin infection
- Period prevalence of Sarcopenia: It is the proportion of a population that has sarcopenia at some time during a given period (March. 2018-September 2018), and includes people who already have sarcopenia at

the start of the study period as well as those who acquire it during that period.

STATISTICAL ANALYSIS

Continuous variables will be expressed as median (range). The Mann–Whitney U test was used to evaluate the significance of differences in median values. The chi-square test or Fisher's exact test will be used to compare differences in categorical variables between groups. Possible predictors of sarcopenia will be evaluated first with a univariate logistic regression analysis, and a multivariate logistic analysis will be then conducted with variables that were significant in the univariate analysis. The prognostic factors of patients with liver cirrhosis will be analyzed by a Cox proportional hazards regression model. Survival rates will be estimated with the Kaplan-Meier method, and compared between groups by the log-rank test. The correlation between CTP, MELD and sarcopenia will be done using Pearson correlation coefficient. All analyses will be carried out using SPSS version 21 software. $P < 0.05$ was considered statistically significant.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

No

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached here with

LIST OF REFERENCES

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Proforma

Name:	**S.NO**
Address:	**MRD.NO**
Mobile No:	**Age/Sex:**
Date of Admission:	**Date of Discharge:**

1) **HISTORY**

1) Presenting complaints

Symptoms	*Duration*
1)	
2)	
3)	

1.1) ***Past history*** – H/o Cirrhosis since

_____

1.2) H/o Bleed _____

Signature of Candidate **Signature of Supervisor**

H/o Ascites _____

H/o Hepatic encephalopathy _____

H/o Diabetes, Hypertension _____

H/o Ischemic heart disease, _____

Gait Speed (m/s):_____

Hand grip strength: _____

L3 SMI (cm^2 / m^2): _____

DIAGNOSIS: _____

_____

_____

Lab Investigation:

Parameter	***Baseline***
Hb (g/dl)	
TLC	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	

Signature of Candidate **Signature of Supervisor**

Platelets	
PTI (INR)	
Glucose	
Blood urea	
Creatinine (mg/dl)	
Serum Sodium (meq/L)	
Serum Potassium (meq/L)	
Serum Chloride (meq/L)	
Bilirubin–T (mg/dl)	
Bilirubin-D (mg/dl)	
SGOT (U/L)	
SGPT (U/L)	
ALP (U/L)	
T Protein (g/dl)	
Albumin	
Urine R/E	
Urine C/S	

Signature of Candidate **Signature of Supervisor**

Blood C/S	

MELD Score: _____

CTP Score: _____

Chest XRay PA view -

_____

Ultrasound abdomen/CT abdomen-

_____

_____

Upper GI Endoscopy-

_____

_____

Patient Follow up at 12 months:

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS"**

The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out.

I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"SARCOPENIA DECREASES THE SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ